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Some Effects of Digoxin upon the Heart and Circulation in Man

Digoxin in Chronic Cor Pulmonale

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The effects of acute digitalization upon the dynamics of the circulation were observed in patients with chronic cor pulmonale, using the technic of cardiac catheterization. The state of the circulation was further investigated in the same patients following recovery from failure. The mode of action of intravenous digoxin is discussed, and a tentative concept of the pathogenesis of chronic cor pulmonale is presented.

As the study of the action of cardiac glycosides on human circulation continues, it becomes increasingly apparent that the effect of such drugs depends not only upon their inherent pharmacologic activity but also upon the physiologic state of the patients receiving them. Considerable attention must, therefore, be given to an analysis of the basic hemodynamic alterations in the groups of patients to be studied in order to insure a reasonable interpretation of drug effects. The reaction to digoxin of one group of patients with the same circulatory abnormality, namely left ventricular failure, has already been reported.[1] In this paper the effects of digoxin in patients with right heart failure secondary to chronic cor pulmonale will be presented and discussed.

In patients with left ventricular failure the sequence of events producing the hemodynamic abnormalities are fairly well understood: failure of the left ventricle results in elevation of pulmonary venous pressure and ultimately in pulmonary artery hypertension. In right heart failure from chronic cor pulmonale the problem is much more complex. Chronic lung disease, by anatomic or physiologic alteration of the pulmonary vascular bed, frequently creates pulmonary arterial hypertension. Indeed, the latter condition may be the sole evidence of involvement of the circulation in lung disease. In some cases this pulmonary hypertension may eventually result in enlargement and even failure of the right ventricle. This syndrome is recognized as chronic cor pulmonale, or heart disease due to lung disease. However, in addition to pulmonary hypertension there are in some cases other changes, such as anoxia, hypervolemia and polycythemia imposed upon the circulation by the chronic pulmonary disease. The mechanisms whereby these factors influence the pulmonary circulation and the cardiac function are not clearly understood. It is obvious that a complete examination of the problem of the heart in chronic lung disease is greatly to be desired. Such a study is at present in progress and will be the subject of a later report.[2] An investigation of the effects of a circulatory

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drug in chronic cor pulmonale and also in simple pulmonary hypertension secondary to chronic lung disease, however, may not only further elucidate the action of the medication itself, but may contribute valuable information to the entire problem of the heart in chronic pulmonary disease.

This report is concerned with the acute, early effects of digoxin in patients with cor pulmonale in cardiac failure, patients with cor pulmonale who were no longer in cardiac failure, and patients with simple pulmonary hypertension secondary to lung disease. In addition, the long-term results of digitalization and associated therapy in patients with right heart failure and cor pulmonale were investigated.

Some patients with heart failure of varying etiologies other than cor pulmonale may, in addition, be suffering from chronic pulmonary disease. Pathologic changes resulting from the latter condition may produce pulmonary hypertension by restricting the pulmonary vascular bed and cause such additional complications as anoxia, polycythemia and hypervolemia, which may further embarrass the circulation. In an attempt to clarify this complicated hemodynamic problem, the effect of digoxin was followed in 2 such patients.

Material for Study

The patients presented in this report have been divided into four major groups: (1) patients with chronic cor pulmonale in cardiac failure, (2) patients with chronic cor pulmonale no longer in cardiac failure, (3) patients with pulmonary hypertension secondary to chronic lung disease and no evidence of heart disease and (4) patients with chronic lung disease and heart disease of varying etiologies other than cor pulmonale.

The clinical diagnosis of chronic lung disease was confirmed by extensive respiratory studies performed according to methods previously described.[3] The results of these studies are listed in table 1.

The first group (tables 2 and 3) consists of 5 patients with chronic cor pulmonale in cardiac failure who fulfill the accepted criteria[4] for the diagnosis of chronic cor pulmonale, namely the presence of chronic pulmonary disease, evidence of right heart enlargement or failure, marked cyanosis, and no other demonstrable etiology of their heart disease. The individual pulmonary diagnoses of these subjects can be found in table 2. At the time of their initial cardiac catheterization, all five patients presented the same clinical picture: marked cyanosis, severe dyspnea, profound right heart failure and normal sinus rhythm or sinus tachycardia. There was moderate cardiac enlargement in all and the pulmonic second sound was either equal to or greater than the aortic second sound. No murmurs were heard. In 3 patients the electrocardiogram suggested right ventricular hypertrophy, while the electrocardiogram of a fourth (A.D.) showed abnormal T waves in Leads II and III and V_4 and V_5 but no other specific abnormalities. A fifth patient (J.B.) had bundle branch block, type unclassified.

It can be seen from table 1 that all the subjects had pulmonary insufficiency, as evidenced by a reduction in vital capacity, maximum breathing capacity, and arterial oxygen saturation. The residual air was greater than predicted and contributed 36 per cent or more to the total lung volume. These findings, associated with a high arterial carbon dioxide tension and a high alveolar nitrogen after seven minutes of pure oxygen breathing, confirm the presence of pulmonary emphysema.[5]

In all 5 patients, a second hemodynamic study was undertaken at a time when the maximum effect of combined therapy appeared evident. Pulmonary function tests were also repeated at the same time.

The second group (tables 4 and 5) consists of 3 patients with chronic cor pulmonale who had recently been in cardiac failure, but who were not in failure at the time of the drug study. All had chronic pulmonary emphysema and one (L.B.) had silicosis of the conglomerate type. At the time of admission there was evidence of bronchitis, bronchorrhea, moderate right heart failure and cyanosis in 2 patients (L.B. and T.D.). In the third (L.P.) there was no evidence of broncho-pulmonary infection. In 2 of the 3 patients (L.B. and T.D.) the second pulmonic sound was greater than the second aortic sound, while in the third (L.P.) the second pulmonic sound was equal to the second aortic sound. All 3 had either normal sinus rhythm or sinus arrhythmia.

The electrocardiograms of these subjects revealed that one (L.P.) had inverted T waves in precordial Leads V_1 to V_4 and no evidence of right ventricular hypertrophy, another (L.B.) showed a double peak of R in Lead V_1 and inverted T waves in standard Leads II and III, and in the third (T.D.) the precordial leads were suggestive of right ventricular hypertrophy.

None of these patients was given digitalis prior to cardiac catheterization. At the time of the drug study, however, all signs of cardiac failure had disappeared and roentgenographic examination revealed a reduction in heart size as compared with the admission films, but all 3 still had enlarged hearts and dilated pulmonary arteries.

TABLE 1.—*Summary of Measurements of Pulmonary Function in the Twelve Cases Reported*

Case	Time	Vital capacity		Residual Air		RA/TC × 100	Maximum Breathing Capacity (% of Pred.)	Index of Intrapul. Mix. Alveolar N_2* (%)	Arterial Blood	
		cc. Obs.	% of Pred.	cc. Obs.	% of Pred.				O_2 Sat. At Rest (%)	pCO_2† At Rest (mm. Hg)
I. Five Patients with Cor Pulmonale in Cardiac Failure										
A.D.										
BSA 1.56	1 Wk. after 1st Cath.	2568	88	1824	180	42	51	3.1	78	53
Wt. 63.0										
BSA 1.55	2nd Cath.	2590	88	1371	133	36	70	1.1	83	46
Wt. 55.3										
B.Br.										
BSA 1.61	1st Cath.	1363	40	1982	165	59	23	5.3	61	69
Wt. 59.0										
BSA 1.55	2nd Cath.	2226	66	2046	170	48	32	3.2	91	41
Wt. 53.8										
BSA 1.54	3rd Cath.	2684	79	2733	228	51	53	3.9	90	47
Wt. 53.9										
J.B.										
BSA 1.53	2nd Cath.	1916	59	1720	165	47	77	2.5	85	52
Wt. 50.8										
B.Bu.										
BSA 1.30	1st Cath.	1095	41	1407	152	56	—	3.4	76	58
Wt. 40.0										
BSA 1.26	2nd Cath.	1260	47	1280	139	51	—	2.4	88	51
Wt. 37.2										
T.A.										
BSA 1.78	1st Cath.	1440	40	—	—	—	19	—	76	61
Wt. 72.5										
BSA 1.57	2nd Cath.	3579	100	3091	195	46	40	9.3	91	61
Wt. 51.8										
II. Three Patients with Cor Pulmonale, Recently in Cardiac Failure, not in Failure at Time of Study										
L.P.										
BSA 1.63	Cath.	1701	51	4690	440	73	13	11.3	83	55
Wt. 62.3										
L.B.										
BSA 1.77	Cath.	1836	48	2375	198	57	47	4.4	87	57
Wt. 68.5										
T.D.										
BSA 1.46	3rd Cath.	1332	38	4463	440	77	31	6.1	85	59
Wt. 47.8										
III. Two Patients with Pulmonary Hypertension, Never in Cardiac Failure										
M.M.										
BSA 1.55	Cath.	1896	53	1914	168	50	50	4.8	93 (88)‡	48
Wt. 52.5										
J.McC.										
BSA 1.64	Cath.	2366	59	3075	237	57	33	4.0	93 (67)‡	52
Wt. 56.0										

Studies of pulmonary function (table 1) confirmed the diagnosis of emphysema and revealed advanced pulmonary insufficiency.

The third group (tables 6 and 7) consists of 2 patients with pulmonary hypertension and no evidence of heart disease. Both had chronic pulmonary emphysema and one (M.M.) in addition had evidence of the conglomerate type of silicosis (table

TABLE 1.—*Continued*

Case	Time	Vital Capacity		Residual Air		$\frac{RA}{TC} \times 100$	Maximum Breathing Capacity (% of Pred.)	Index of Intrapul. Mix. Alveolar N_2* (%)	Arterial Blood	
		cc. Obs.	% of Pred.	cc. Obs.	% of Pred.				O_2 Sat. At Rest (%)	pCO_2† At Rest (mm. Hg)
IV. Two Patients with Chronic Pulmonary Disease and (a) Arteriosclerotic Heart Disease and (b) Arteriosclerotic and Hypertensive Heart Disease										
(*a*) *J.P.* BSA 1.84 Wt. 69.6	Cath.	2816	66	2044	147	42	57	2.6	92	(39.3)§
(*b*) *W.H.* BSA 1.90 Wt. 79.3	1st Cath.	1880	49	—	—	—	32	—	80	44
BSA 1.89 Wt. 77.8	2nd Cath.	2660	69	2667	169	50	49	4.9	90	41

Obs. = Observed.
Pred. = Predicted.
$\frac{RA}{TC} \times 100$ = Ratio of Residual Air to Total Capacity.
Index of Intrapul. Mix. = Index of intrapulmonary mixing.
* Alveolar nitrogen per cent after seven minutes pure oxygen breathing.
† Normal value 39.4 ± 2.8 mm. Hg.
BSA = Body surface area in square meters.
Wt. = Weight in Kilograms.
Cath. = At time of catheterization.
‡ After exercise.
§ Carbon dioxide content, Vols. %. (Normal = 49.2 ± 3.2.)

6). Cardiac examination was unimpressive. Normal sinus rhythm was present in both. In one of these patients (J.McC.) the second pulmonic sound was equal to the second aortic sound, and in the other (M.M.) the second pulmonic sound was greater than the second aortic sound. The presence of cyanosis was questionable in both subjects. There were no signs of cardiac failure.

In one patient (J.McC.) the electrocardiogram was entirely normal and the second (M.M.) had moderate right axis deviation. In neither was there evidence of right ventricular hypertrophy. The cardiac silhouettes in both were normal in size and vertical in position. The left descending branch of the pulmonary artery in one patient (J.McC.) was prominent. In the patient with silicosis (M.M.) the left upper cardiac contour was obscured by the pulmonary fibrosis.

It is of interest that the results of the pulmonary function studies in these subjects, as listed in table 1, differed from those of the first two groups with advanced pulmonary insufficiency in only one respect, namely that in this group the arterial oxygen saturation was only slightly reduced at rest.

In the *fourth group* (Tables 8 and 9) one (J.P.) of the 2 patients had pulmonary emphysema, arteriosclerotic heart disease and congestive failure. The second (W.H.) had silicosis of the diffuse type, pulmonary emphysema, hypertensive and arteriosclerotic heart disease and congestive failure. At the time of study both presented the same clinical picture as the patients with cor pulmonale in failure. There was marked cardiac enlargement, but only one (J.P.) had enlargement of the pulmonary artery. In one patient (J.P.) the second pulmonic sound was equal to the second aortic sound and there was a harsh apical systolic murmur, and in the other (W.H.) the second aortic sound was greater than the second pulmonic sound and there was a soft basal systolic murmur. Both of these patients had sinus rhythm with premature auricular and ventricular contractions. The electrocardiogram of one subject (J.P.) showed no abnormal deviation of the electrical axis, while in the second (W.H.) there was left axis deviation, left bundle branch block, and absent R waves over the left precordium. It was of interest that in both these patients the Q-T interval was prolonged, while this interval was normal in all of the patients previously discussed.

It can be seen from the data in table 1 that both patients had pulmonary insufficiency and differed from the previous groups in one important respect, namely that the arterial blood carbon dioxide tension was within normal limits.

TABLE 2.—*Measurements of the Circulation in Five Patients with Chronic Cor Pulmonale in Cardiac Failure; During Acute Digitalization Studies and Following Recovery*

Case	Time (Min.)	Brachial Artery (mm. Hg)		Pulmonary Artery (mm. Hg)		Right Ventricle (mm. Hg)	Cardiac Output (L/Min.)	Stroke Volume (cc.)	Heart Rate (Beats per Min.)
		s/d	m	s/d	m	s/d			
First Study									
A.D. Female, 55 years, B.S.A. 1.65, Bronchial asthma. Chronic bronchitis. Pulmonary emphysema, minimal (Ayerza's syndrome). Cor pulmonale. EH. NSR. CHF. IHC.	Control	140/75	103			62/10			97
		160/71	95	63/29	44	63/11	10.0	103	97
	7*	147/77	106	62/22	41	62/8			88
	14	150/74	107	62/22	41	62/8			85
	29	152/72	104	65/22	41	65/8			88
	38	161/74	110	66/23	43	66/9			88
	46	152/71	102	69/23	44	69/5			88
	53						11.6	130	88
	60	144/68	96	73/23	44	—			88
	73	145/67	99	69/25	42	69/5			88
	82						11.6	130	88
	86	159/75	108	74/26	45	74/4			88
Two and one-half months after first study									
B.S.A. 1.55		142/79	106	31/13	20	31/2	6.0	78	65
		138/77	102	35/13	21				65
				31/15	22	31/1			65
First Study									
B.Br. Male 52 years, B.S.A. 1.61, Bronchial asthma. Chronic pulmonary emphysema, moderate. Cor pulmonale. EH. NST. CHF. IVD.	Control	—	—	72/36	49	72/15			109
		103/69	82	72/35	49	72/13	7.14	67	108
		100/68	82	72/36	48	72/13			109
	6*	116/73	91	68/32	46	68/12			109
	17	106/72	88	68/30	45	68/10			109
	32	112/66	85	78/29	49	78/11			109
	41						6.38	59	108
	49	127/73	94	78/29	49	78/9			109
	61	—	—	73/31	49	73/7	8.08	75	108
	67	174/95	119	79/30	52	79/9			109
	76	163/88	109	76/26	46	76/5			109
Two weeks after first study									
B.S.A. 1.55		117/71	89	35/15	24				93
		132/80	99	34/17	24		5.09	55	93
		119/70	89	38/19	26	38/0	5.52	59	93
Four and one-half weeks after first study									
B.S.A. 1.54		109/62†	80	26/11	15	26/0	5.12	56	93
		113/64	85	26/7	13	26/0			
First Study									
J.B. Male, 60 years, B.S.A. 1.62, Chronic bronchitis. Bronchiectasis. Pulmonary fibrosis. Chronic pulmonary emphysema, moderate. Cor pulmonale. EH. NSR. CHF. BBB. IVD.	Control	114/78	82	82/42	55				100
		117/78	84	85/37	55		6.54	67	100
				81/37	55	81/16			100
		112/66	82	82/35	51	82/17			100
	7‡	124/70	89	87/36	53	87/16			100
	17	132/74	93	83/33	53	83/13			100
	28	139/78	97	91/27	53	91/12			100
	36	129/68	89	81/33	48	81/11			100

TABLE 2.—*Continued*

Case	Time (Min.)	Brachial Artery (mm. Hg)		Pulmonary Artery (mm. Hg)		Right Ventricle (mm. Hg)	Cardiac Output (L/Min.)	Stroke Volume (cc.)	Heart Rate (Beats per Min.)
		s/d	m	s/d	m	s/d			
First Study—*Continued*									
J.B. Male—*Cont.*	42						8.57	88	98
	52	126/66	86	82/33	50	82/8			104
	60	130/70	91†	89/36	57	89/9			107
	64						7.60	84	99
	67	128/70	89	87/36	55	87/6			110
Five and one-half weeks after first study									
B.S.A. 1.53		95/53	70	33/12	20		5.98	79	76
		88/51	65	30/12	19	30/1			75
First Study									
B.Bu. Female, 35 years, B.S.A. 1.30, Chronic pulmonary tuberculosis—IIIC active. Hydropneumothorax—right. Morphine addiction. Multiple small pulmonary emboli. Pulmonary emphysema, moderate. Cor pulmonale. EH. NST. CHF. IVD.‖	Control	147/89	112	79/39	60				104
		140/83	107	77/43	60	77/12	5.76	53	109
	6§	162/94	124	82/44	63				109
	21	163/91	116	86/41	60				109
	29						5.52	49	113
	31	171/96	127	84/43	64				115
	40	123/67	90	83/43	63				115
	44						6.06	52	116
	50	156/88	113	84/44	61	84/7			115
Two and one-half weeks after first study									
B.S.A. 1.26		116/74	91	55/25	37				100
		135/88	107	54/27	37		5.13	51	100
		131/80	103	52/26	37	52/1	5.25	53	100
First Study									
T.A. Male, 55 years, B.S.A. 1.78, Silicosis. Chronic pulmonary emphysema, moderate. Cor pulmonale. EH. NSR. CHF. IIIC.	Control	129/82	94	63/32	45				88
							4.25	45	94
		122/78	92	60/31	38	60/10			88
				59/31	41	59/12			102
				60/28	38	60/10			90
	6*	124/78	100	65/32	43				93
	9	135/85	109	64/29	41				88
	26	135/78	100	70/29	42				88
	32						5.28	60	88
	34	132/77	100	72/31	45				88
	47						4.96	52	95
	50	137/80	104	75/33	50				93
	60	132/80	104	67/29	42				90
	67						4.98	51	98
	76	135/79	100	70/32	46	70/4			93
Two weeks after first study									
B.S.A. 1.57		133/89	105	28/12	18		3.36	43	75
		114/80	89	28/12	18	28/−5	3.74	47	75

s = systolic; d = diastolic; m = mean.
B.S.A. = Body surface area.
EH = Enlarged heart.
NSR = Normal sinus rhythm.
NST = Normal sinus tachycardia.
CHF = Congestive heart failure.
BBB = Bundle branch block.
* Time after start of injection of 1.5 mg. digoxin.
† Femoral artery pressures.
‡ Time after start of injection of 1.25 mg. digoxin.
§ Time after start of injection of 1.0 mg. digoxin.
‖ Diagnosis confirmed by autopsy.

TABLE 3.—*Physiologic Data Concerning Cardiac Output and Blood Volume in Five Patients with Chronic Cor Pulmonale in Cardiac Failure; During Acute Digitalization Studies and Following Recovery*

Case	Time (Min.)	Cardiac Index (L/Min./M² BSA)	Oxygen Consumption (cc./Min./M² BSA)	AV Oxygen Diff. (Vol. %)	Arterial Blood Oxygen			Peripheral Resistance (dynes-sec.-cm.⁻⁵)	Blood Volume		
					Cont. (Vol. %)	Cap. (Vol. %)	Sat. (%)		TBV (cc./M²BSA)	PV (cc./M²BSA)	H′ crit (%)
					First Study						
A.D.	Control	6.06	170	2.8	12.3	20.5	60	720	6050	2043	66
	53*	7.05	176	2.5	11.1	20.4	55	625			
	82	7.04	162	2.3	12.3	20.3	61	725			
					Two and one-half months after first study						
		3.87	143	3.7	15.1	18.4	83	1385	3690	1900	48
					First Study						
B.Br.	Control	4.43	160	3.6	12.7	21.3	61	797	5250	1610	69
	41*	3.96	170	4.3	13.7	21.8	64	930			
	62	5.02	181	3.6	13.6	22.0	63	1007			
					Two weeks after first study						
		3.28	155	4.7	23.1	26.0	91	1560	3955	1270	69
		3.58	157	4.4	23.0	25.9	90	1285			
					Four and one-half weeks after first study						
		3.33	136	4.1	16.6	18.9	90	1250	3080	1630	47
					First Study						
J.B.	Control	4.04	157	3.9	8.5	15.7	55	885	4125	1896	54
	42†	5.29	148	2.8	10.4	16.8	63	738			
	64	4.69	155	3.3	10.5	17.0	64	884			
					Five and one-half weeks after first study						
		3.91	146	3.8	14.9	17.8	85	670	4035	2100	48
					First Study						
B.Bu.	Control	4.42	181	4.1	11.4	15.5	76	1360	3560	2030	43
	29‡	4.25	178	4.2	11.9	15.8	77	1650			
	44	4.66	181	3.9	11.5	15.6	75	1400			
					Two and one-half weeks after first study						
		4.07	167	4.1	12.5	14.6	88	1650	3060	1815	41
		4.17	167	4.0	12.2	14.7	85	1570			
					First Study						
T.A.	Control	2.39	122	5.1	13.1	17.7	76	1745			48
	32*	2.97	124	4.2	12.8	—	—	1515			
	47	2.79	131	4.7	13.5	17.7	78	1680			
	67	2.80	126	4.5	13.5	18.0	76	1640			
					Two weeks after first study						
		2.14	113	5.3	17.0	19.0	91	2500	3995	2075	48
		2.38	119	5.0	16.7	18.9	90	1950			

TBV = Total blood volume.
PV = Plasma volume.
* Time after start of injection of 1.5 mg. digoxin.
† Time after start of injection of 1.25 mg. digoxin.
‡ Time after start of injection of 1.0 mg. digoxin.

TABLE 4.—*Measurements of the Circulation in Three Patients with Chronic Cor Pulmonale, Recently in Cardiac Failure, not in Failure at Time of Study*

Case	Time (Min.)	Brachial Artery (mm. Hg)		Pulmonary Artery (mm. Hg)		Right Ventricle (mm. Hg)	Cardiac Output (L/Min.)	Stroke Volume (cc.)	Heart Rate (Beats per Min.)
		s/d	m	s/d	m	s/d			
L.P. Male, 48 years, B.S.A. 1.63. Chronic pulmonary emphysema, obstructive, advanced. Cor pulmonale. EH. NSR. IIB.	Control			35/17	23	35/0			83
				34/17	28	34/0			83
		109/68	83	35/17	24	35/0	5.84	70	83
		103/65	83	36/14	23				83
		96/63	78	38/14	24	38/0			80
	2*	118/73	89						83
	8	118/70	85	41/16	25	41/1			83
	15	120/71	89	39/17	26	39/0			83
	22	120/70	87	40/17	26	40/−1			78
	35						5.79	70	83
	43			39/18	25	39/−1			83
	49	117/70	88	39/17	26	39/3			83
	63	115/68	86	36/13	26	36/−1			83
	75						5.65	68	83
	81	112/66	85	37/15	26	37/−2			88
	91			43/18	28	43/0			83
L.B. Male, 54 years, B.S.A. 1.77. Silicosis. Chronic pulmonary emphysema, moderate. Cor Pulmonale. EH. SA. IIB.	Control	120/75	93	43/19	32				85
				50/21	36	50/0	5.32	63	84
		138/90	111	49/22	36				83
	7*	158/90	119	50/20	35	50/0			83
	17	146/99	122	50/22	35	49/−1			83
	30	152/96	122	48/20	34	48/−1			83
	32						5.27	63	84
	40	152/95	118	48/23	34	48/−1			83
	55	146/90	115	44/22	34	44/−1			83
	61						5.15	66	85
	65	158/99	126	45/21	34	45/−1			85
First Study									
T.D. Male, 48 years, B.S.A. 1.48. Chronic pulmonary emphysema, obstructive, advanced. Cor Pulmonale. EH. NSR. IIB.	Control	116/72	91	43/21	30	43/5			96
		121/75	98	40/19	28	40/4	5.70	59	98
				41/20	31	41/4			96
	5†	122/75	93	42/21	30	42/3			92
	11	130/76	96	46/18	32	46/3			90
	30	136/77	103	44/18	31		6.15	70	88
	41	132/75	96	43/17	28	43/3			88
	53	140/76	104	41/17	28	41/5			88
	65						5.82	69	
	70	141/80	104	44/20	28	44/3			83
Two weeks after first study									
B.S.A. 1.45		117/70	86			39/1	4.76	50	96
		132/80	103			41/3	4.47	47	96
Seven months after first study									
B.S.A. 1.46		127/80	94			−/−2	4.98	57	88
							4.99	57	88

s = systolic; d = diastolic; m = mean.
B.S.A. = Body surface area.
EH = Enlarged heart.
SA = Sinus arrhythmia.
NSR = Normal sinus rhythm.

* Time after start of injection of 1.5 mg. digoxin.
† Time after start of injection of 1.25 mg. digoxin.

Method of Study

Procedure. The method of investigation used in this study was identical to that described in the previous report on digoxin.[1] Digoxin, 1.0 to 1.5 mg. in 30 cc. of physiologic saline was injected through the catheter into the pulmonary artery over a five minute period.

In view of recent experiences in this laboratory, certain precautions in the handling of the intra-arterial needle have been deemed necessary. On three occasions during the past two years a vasovagal syndrome has been produced at the time of insertion or removal of the brachial artery needle. This condition persisted for only a short time. In none of these patients could the incident be attributed to the cardiac catheter, as in one case it had not been inserted and in the other two it had been removed. Because complete A-V block and marked bradycardia may accompany this syndrome, the electrocardiogram should be carefully observed whenever the arterial needle is manipulated. Liberal infiltration of the puncture site with novocain before the insertion and the removal of the indwelling needle may prevent these complications.

Interpretation of Results. In order to evaluate the changes produced by medication, control data were analyzed to determine the range of variation expected with the technics employed. These data have been presented in detail in a previous communication.[1] It was concluded that any cardiac output change greater than 9 per cent of the control measurement could be ascribed to the action of the drug, provided that the oxygen consumption remained constant. The mean blood pressure variation in the right ventricle and pulmonary artery was 2.0 mm. Hg with a maximum deviation of 5.0 mm. Hg. It should be noted that there is marked respiratory variation in the blood pressure tracings of patients with chronic pulmonary disease. For this reason, control pressures in such cases vary to a greater extent than do those of other patients. It is, therefore, essential that the blood pressure tracings during at least two complete respiratory cycles be analyzed.

The upper limit of normal pressure values used in this laboratory are the following: pulmonary artery and right ventricular systolic pressure = 30 mm. Hg, pulmonary arterial diastolic pressure = 10 mm. Hg, mean pulmonary arterial pressure

Table 5.—*Physiologic Data Concerning Cardiac Output and Blood Volume in Three Patients with Chronic Cor Pulmonale, Recently in Cardiac Failure, not in Failure at Time of Study*

Case	Time (Min.)	Cardiac Index (L/Min./M² BSA)	Oxygen Consumption (cc/Min./M² BSA)	AV Oxygen Diff. (Vol. %)	Arterial Blood Oxygen			Peripheral Resistance (dynes-sec.-cm.$^{-5}$)	Blood Volume		
					Cont. (Vol. %)	Cap. (Vol. %)	Sat. (%)		TBV (cc/M² BSA)	PV (cc/M² BSA)	H′ crit (%)
L.P.	Control	3.58	154	4.3	16.5	20.0	83	1135	3650	1595	56
	35*	3.55	149	4.2	16.5	—	—	1200	—	—	—
	75	3.47	149	4.3	16.6	19.9	85	1210	—	—	—
L.B.	Control	3.01	141	4.7	20.9	23.8	89	1670	4180	1655	60
	32*	2.97	146	4.9	20.2	23.4	88	1820			
	61	2.91	142	4.9	20.3	23.2	89	1957			
T.D.	Control	3.85	142	3.7	16.3	19.6	82	1270	4580	2110	54
	30†	4.16	137	3.3	16.0	20.0	82	1340	—	—	—
	65	3.93	134	3.4	16.7	19.6	84	1215	—	—	—
Two weeks after first study											
		3.28	138	4.2	16.7	18.7	90	1450	3700	1650	55
		3.08	132	4.3	16.7	18.6	91	1825	—	—	—
Seven months after first study											
		3.41	147	4.3	16.2	18.4	91	1550	—	—	47
		3.42	150	4.4	16.2	—	—	1550			

* Time after start of injection of 1.5 mg. digoxin.
† Time after start of injection of 1.25 mg. digoxin.
TBV = Total blood volume.
PV = Plasma volume.

TABLE 6.—*Measurements of the Circulation in Two Patients with Pulmonary Hypertension never in Cardiac Failure*

Case	Time (Min.)	Brachial Artery (mm. Hg)		Pulmonary Artery (mm. Hg)		Right Ventricle (mm. Hg) s/d	Cardiac Output (L/Min.)	Stroke Volume (cc.)	Heart Rate (Beats per Min.)
		s/d	m	s/d	m				
M.M. Male, 46 years, B.S.A. 1.55. Silicosis. Chronic pulmonary emphysema, moderate. Pulmonary hypertension.	Control	70/52	62	29/13	21				78
		71/48	58	29/13	20				83
		79/56	66	29/13	21	29/4			83
		80/58	64			28/3			83
		87/61	72	28/13	20	28/3	5.07	61	88
				30/13	21				83
	6*	92/63	75	32/13	23	32/4			83
	11	93/63	74	32/14	23				83
	17						4.98	60	
	24	95/63	77	30/14	22	30/1			83
	35	91/60	75	33/13	23	33/1			83
	42	91/60	74	32/14	23	32/1			83
	52	102/65	82	35/14	23				83
	55						5.65	68	
	60	105/66	79	35/15	24	35/1			83
J.McC. Male, 72 years, B.S.A. 1.64. Chronic pulmonary emphysema, obstructive, advanced. Pulmonary hypertension. Generalized Arteriosclerosis.	Control	164/85	113	41/9	24	41/2			85
		160/79	108	43/10	25	43/2	5.65	65	87
		155/79	108	42/12	26				88
	5†	174/91	120	41/12	25	41/3			83
	18	—	115	43/10	27	43/2			78
	39						5.69	73	78
	43	170/78	110	40/7	23	40/2			74
	53	176/80	108	42/11	24	42/2			75
	62						5.98	79	76
	68	175/83	117	—	—	39/2			75

* Time after start of injection of 1.0 mg. dioxin.
† Time after start of injection of 1.5 mg. digoxin.
s = systolic; d = diastolic; m = mean.
B.S.A. = Body surface area.

TABLE 7.—*Physiologic Data Concerning Cardiac Output and Blood Volume in Two Patients with Pulmonary Hypertension, Never in Cardiac Failure*

Case	Time (Min.)	Cardiac Index (L/Min./M² BSA)	Oxygen Consumption (cc./Min./M² BSA)	AV Oxygen Diff. (Vol. %)	Arterial Blood Oxygen			Peripheral Resistance (dynes-sec.-cm.⁻⁵)	Blood Volume		H′ crit (%)
					Cont. (Vol. %)	Cap. (Vol. %)	Sat. (%)		TBV	PV	
									(cc./M² BSA)		
M.M.	Control	3.27	141	4.3	16.9	18.2	94	1140	3310	1885	43
	17*	3.20	154	4.8	17.0	18.3	94	1250	—	—	—
	55	3.64	145	4.0	17.2	18.3	95	1130	—	—	—
J.McC.	Control	3.45	148	4.3	18.5	20.0	94	1530	3745	1860	50
	39†	3.47	146	4.2	18.1	19.6	94	1550	—	—	—
	62	3.64	146	4.0	18.1	19.7	93	1565	—	—	—

* Time after start of injection of 1.0 mg. digoxin.
† Time after start of injection of 1.5 mg. digoxin.
TBV = Total blood volume.
PV = Plasma volume.

TABLE 8.—A. *Measurements of the Circulation in One Patient with Chronic Pulmonary Disease and Arteriosclerotic Heart Disease*

Case	Time (Min.)	Brachial Artery (mm. Hg) s/d	Brachial Artery (mm. Hg) m	Right Ventricle (mm. Hg) s/d	Cardiac Output (L/Min.)	Stroke Volume (cc.)	Heart Rate (Beats per Min.)
J.P. Male, 66 years, B.S.A. 1.84. Pulmonary emphysema, moderate. ASHD. EH. Calcification of aorta. CS. MF. NSR with VPC's. CHF. TI. IVD.	Control	119/86	98	46/14			88
		123/83	99	44/16	1.80	22	96
	7*	126/85	98	59/16			78
	10	109/68	82	51/13			78
	21				2.10	28	75
	32	135/88	103	57/14			75
	39	130/90	103	55/14			78
	51	137/86	108	57/14			75
	61	136/88	105	59/15			75
	67				2.17	27	80
	70	142/87	110	66/16			83

B. *Measurements of the Circulation in One Patient with Chronic Pulmonary Disease and Hypertensive Cardiovascular Disease and Arteriosclerotic Heart Disease*

Case	Time (Min.)	Brachial Artery (mm. Hg) s/d	Brachial Artery (mm. Hg) m	Pulmonary Artery (mm. Hg) s/d	Pulmonary Artery (mm. Hg) m	Right Ventricle (mm. Hg) s/d	Cardiac Output (L/Min.)	Stroke Volume (cc.)	Heart Rate (Beats per Min.)
First Study									
W.H. Male, 65 years, B.S.A. 1.90. Silicosis. Pulmonary emphysema. HCVD. ASHD. EH. CS. MF. Old myocardial infarct. SA with APC's, VPC's. CHF. LBBB. IVD.	Control	162/98	117	49/26	36		4.80	50	75–78
		184/113	143	52/29	39	52/11			78–83
		177/103	120			49/9			88–100
	7†	188/118	152	53/28	42	53/11			80
	14	194/119	164	55/24	40	55/11			80
	34	185/105	144	48/18	31	48/6			80
	47	185/110	142	34/11	24	34/4			80
	52						4.79	55	
	62	174/98	132	28/14	21	28/2			80
	69						5.52	67	
	86	164/100	125	30/10	21	30/3			80
Ten days after first study									
B.S.A. 1.89		157/84‡	108	35/19	26		4.38	56	85
		153/92	106	37/13	22				75
		166/93	113	30/11	19	30/−1			83

* Time after start of injection of 1.0 mg. digoxin.
† Time after start of injection of 1.5 mg. digoxin.
‡ Femoral artery pressures.
s = systolic; d = diastolic; m = mean.
B.S.A. = Body surface area.
ASHD = Arteriosclerotic heart disease.
HCVD = Hypertensive cardiovascular disease.
EH = Enlarged heart.
CS = Coronary sclerosis.
MF = Myocardial fibrosis.
TI = Tricuspid insufficiency.
NSR = Normal sinus rhythm.
APC = Auricular premature contraction.
VPC = Ventricular premature contraction.
SA = Sinus arrhythmia.
CHF = Congestive heart failure.
LBBB = Left bundle branch block.

= 15 mm. Hg, right ventricular end diastolic pressure = 5 mm. Hg. The range of variation in cardiac output among normal subjects in liters per minute per square meter of body surface area is between 2.70 and 3.50. Throughout this study the cardiac index was computed on the basis of the patient's body surface area at the time of cardiac catheterization, regardless of whether or not this represented the patient's dry weight. In the presence of edema, computation of the cardiac index gives a lower value than if dry weight is used. When the patient's weight varies between repeated determinations, comparison of cardiac outputs are of more value than are comparisons of cardiac indices. The mean normal values for total blood and plasma volume are respectively, 2900 cc. and 1600 cc. per square meter of body surface area.

TABLE 9.—A. *Physiologic Data Concerning Cardiac Output and Blood Volume in One Patient with Chronic Pulmonary Disease and Arteriosclerotic Heart Disease*

Case	Time (Min.)	Cardiac Index (L/Min./M² BSA)	Oxygen Consumption (cc./Min./M² BSA)	AV Oxygen Diff. (Vol. %)	Arterial Blood Oxygen			Peripheral Resistance (dynes-sec.-cm.⁻⁵)	Blood Volume		
					Cont. (Vol. %)	Cap. (Vol. %)	Sat. (%)		TBV	PV	H′ crit (%)
									(cc./M² BSA)		
J.P.	Control	0.98	100	10.3	19.4	21.1	92	4400	4550	1925	58
	21*	1.14	100	8.8	19.0	20.1	95	3560			
	67	1.18	110	9.3	19.0	19.9	96	4060			

B. *Physiologic Data Concerning Cardiac Output and Blood Volume in One Patient with Chronic Pulmonary Disease and Hypertensive Cardiovascular Disease and Arteriosclerotic Heart Disease*

Case	Time (Min.)	Cardiac Index (L/Min./M² BSA	Oxygen Consumption (cc./Min./M² BSA)	AV Oxygen Diff. (Vol. %)	Arterial Blood Oxygen			Peripheral Resistance dynes sec. cm.⁻⁵	Blood Volume		
					Cont. (Vol. %)	Cap. (Vol. %)	Sat. (%)		TBV	PV	H′ crit (%)
									(cc./M² BSA)		
First Study											
W.H.	Control	2.53	154	6.1	16.2	20.8	80	1770	3980	1765	56
	52†	2.52	143	5.7	15.8	19.7	80	2200			
	69	2.91	145	5.0	16.2	19.8	84	1880			
Ten days after first study											
		2.32	141	6.1	18.0	20.4	90	1980	2470	1265	49

* Time after start of injection of 1.0 mg. digoxin.
† Time after start of injection of 1.5 mg. digoxin.
TBV = Total blood volume.
PV = Plasma volume.

RESULTS

Group I

Acute Digitalization. The first group of patients (tables 2 and 3) with chronic cor pulmonale were in failure at the time of their first cardiac catheterization. Four of the 5 patients had no specific therapy other than bed rest prior to the first catheterization. One (B.Bu.) had received 2 cc. of Mercuhydrin two days prior to the study. In 4 of the 5 patients the control cardiac outputs were significantly higher than the upper limit of normal, while the output of a fifth (T.A.) was lower than normal. All had marked pulmonary hypertension and considerable elevation of the right ventricular end diastolic pressure. Four of the 5 patients had an increase in total blood volume which was accompanied by an increase in plasma volume in all but one (B.Br.).* Three (A. D., B. Br., and J. B.) of the five showed a significant increase in hematocrit. All had a marked reduction in arterial oxygen saturation.

*Unfortunately, an error in technic prevented determination of blood volume in the fifth patient (T. A.).

It was a remarkable and consistent finding that in this group of patients the oxygen capacity and hence the calculated hemoglobin, was not as high as the hematocrit would suggest.

After digoxin, 4 of the 5 patients had an increase in cardiac output ranging from 13 per cent to 31 per cent. The fifth patient (B. Bu.) had only a 6 per cent rise in cardiac output which cannot be considered significant. In one patient (B. Br.) there was an early fall of 10 per cent in cardiac output concomitant with an increase in systemic peripheral resistance and arterial blood pressure, but the cardiac output later rose to 13 per cent higher than the control figure. All 5 patients had a slight but significant rise in their pulmonary artery systolic pressures, which in 4 was unaccompanied by a change in diastolic or mean pressures. The pulmonary artery diastolic pressure of one (B. Br.) fell slightly without change in the mean pressure. In the 3 patients followed for the longest time (in minutes) after digoxin administration the right ventricular end diastolic pressures returned to normal. In the other patients (J. B. and B. Bu.) this pressure had greatly decreased but had not reached a normal level.

In only 2 of the 5 subjects was there any change in the previously normal brachial artery pressure; one (B. Br.) had a marked rise in systolic, diastolic, and mean pressures and in peripheral resistance, and a second (B. Bu.) had a rise in brachial artery systolic pressure alone.

The changes in heart rate were not consistent; in one patient (A. D.) the rate decreased, in 2 (J. B. and B. Bu.) it increased and in 2 other patients (B. Br. and T. A.) it did not change.

The characteristic response to digoxin as seen in one patient (A. D.) had been illustrated in a previous paper.[1] Similar changes may be seen in figure 1, summarizing the findings in another patient (J. B.).

Long Term Effects of Digoxin and Other Therapy. Following the acute digitalization all 5 patients were kept on bed rest and maintained on a daily dose of 0.5 mg. digoxin. Two patients (A. D. and T. A.) received occasional mercurial diuretics. All but 2 (B. Bu. and B. Br.) of the 5 received vaponephrin inhalations three or four times a day, during the interval between the first and second catheterization. Only one subject (A. D.) had several phlebotomies during this period. At the time of the second study, all 5 patients showed remarkable clinical improvement. Dyspnea and cyanosis had markedly decreased, there were no longer any signs of cardiac failure, and all had lost a considerable amount of weight. The cardiac silhouette in all but one (B. Bu.) was markedly reduced in size. The serial roentgenograms of one patient (B. Br.) are seen in figure 2. Respiratory studies revealed improved pulmonary function (table 1) as indicated by an increase

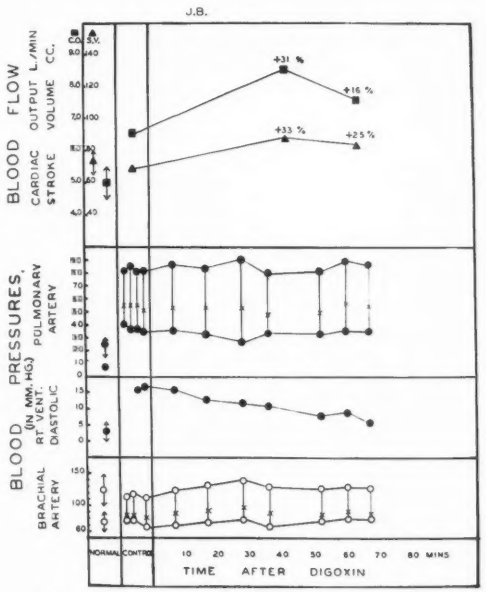


FIG. 1.—Effect of digoxin in right heart failure due to chronic cor pulmonale. (Closed triangles = stroke volume; closed squares = cardiac output; closed circles = pulmonary artery systolic and diastolic, and right ventricular end diastolic pressures; open circles = brachial artery systolic and diastolic pressures; cross marks = mean pressures.)

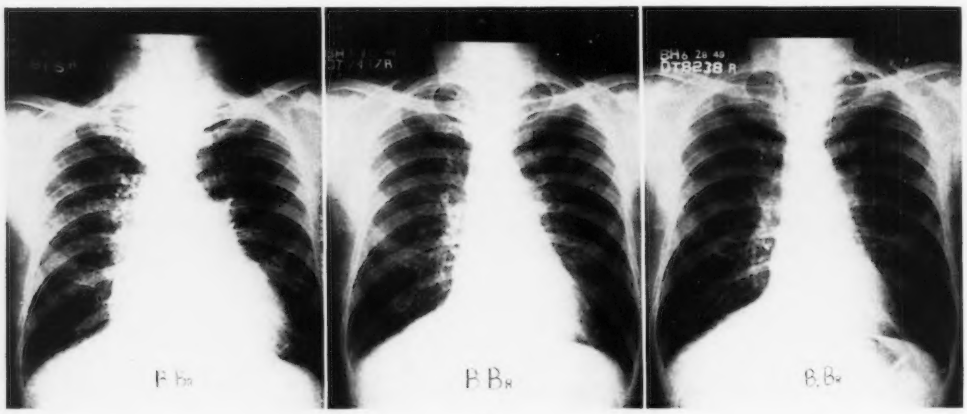
The normal mean values and approximate range of variation are plotted in the first vertical column. Note that (a) the initially elevated cardiac output rose considerably after digoxin, (b) the elevated right ventricular end diastolic pressure returned to normal, and (c) with the increase in stroke volume the pulmonary artery systolic pressure rose.

in vital capacity, maximum breathing capacity and a decrease in residual air to total capacity ratio, and an improvement in the index of intrapulmonary mixing. The arterial blood oxygen saturation had increased strikingly.

Regardless of the type of adjuvant therapy, the main findings in all 5 patients at the time of the second hemodynamic study were strikingly similar (tables 2 and 3). The cardiac output was considerably lower than at the time of the first study. *In every instance the pulmonary artery pressures were markedly reduced as compared to the control values, and in 4 of the patients these pressures were almost normal.* In all 5 patients the right ventricular diastolic was well within normal limits. There was no appreciable change in arterial blood pressure, and in 4 of the 5 the systemic peripheral resistance was higher than before.

The changes in blood volume and hematocrit between the first and second studies were quite variable. The blood volume and hematocrit of the 2 patients (A. D. and B. Br.) who had the largest increase in these determinations at the time of their first catheterization, were reduced but were still significantly above normal at the time of the second catheterization. Only one of these 2 (A. D.) had been repeatedly phlebotomized (total of 4200 cc.) in the interval between studies. One patient (B. Bu.), who had the least elevation of blood volume, had returned to normal, without aid of phlebotomy, at the time of her second study. Another patient (J. B.) had no significant change in blood volume or hematocrit and these values were still moderately elevated. In 4 of the 5 patients, regardless of whether the hematocrit remained the same or fell, the arterial oxygen capacity showed a relative increase as compared to the first study.

One patient (B. Br.), who had been treated with only bed rest and digoxin between his first and second studies, was catheterized a third time, after receiving vaponephrin and having four 500 cc. phlebotomies in two and one-half weeks. At this time, although the blood volume and hematocrit were reduced to normal, the cardiac output, arterial saturation and peripheral resistance were the same as on the second study. The pulmonary artery pressures, which were slightly elevated at the time of the second catheterization, were now entirely normal. In figures 3 and 4 the long term changes in cardiocirculatory and pulmonary function are illustrated in this and another patient (B. Br. and A. D.).



a b c

Patient B.Br.

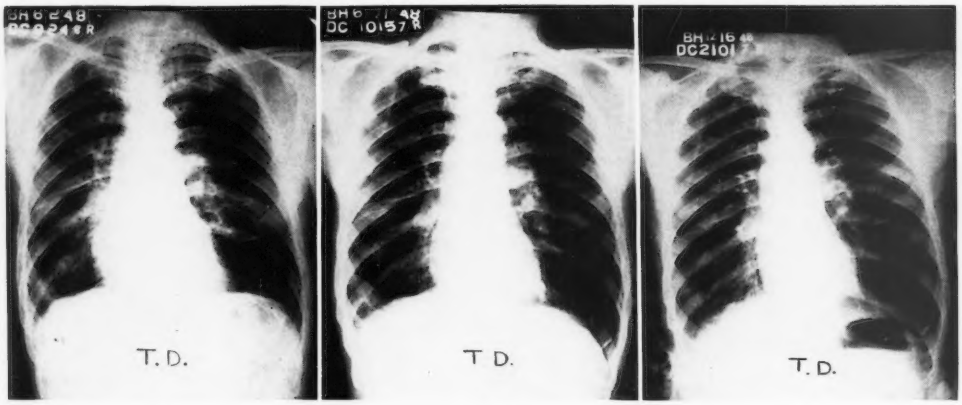
FIG. 2.—Serial roentgenograms in two patients (B.Br. and T.D.) with chronic cor pulmonale. The postero-anterior 6-foot films were taken at the time of each cardiac catheterization: (a) first study, (b) second study, (c) third study. For discussion, see text.

Group II

Acute Digitalization. The 3 patients with chronic cor pulmonale who comprise the second group (tables 3 and 4) were admitted to the hospital in right heart failure. Following two or three weeks of bed rest, and the use of bronchodilators, mercurial diuretics, to which phlebotomy was added in one case (L. P.), all signs and symptoms of cardiac failure disappeared. It was at this time that the cardiac catheterizations were performed. Two of the patients had normal cardiac outputs and stroke volumes, while the cardiac output of the third (T. D.) was slightly elevated. All 3 patients had some degree of pulmonary hypertension but the right ventricular end diastolic pressure was normal. The total blood volume and hematocrits in all 3 were definitely increased. Arterial oxygen unsaturation of moderate degree was present in each of these patients. The arterial oxygen capacity was normal in 2 patients and slightly increased in the third (L. P.).

After acute digitalization there was no change in cardiac output, right heart or pulmonary artery pressures in any of the 3 patients of this group. In 2 patients (L. B. and T. D.) the previously normal brachial artery systolic pressure rose and in one of the 2 (L. B.) there was also a rise in mean pressure and peripheral resistance. There was a decrease in heart rate in only one patient (T. D.).

Long Term Effects of Digoxin and Other Therapy. As can be seen in tables 4 and 5, one patient (T. D.) of this group was restudied two weeks and again seven months after the first catheterization. Between the first and second catheterization he had been maintained on digitalis, bed rest, diuretics and bronchodilators. Thus, after prolonged treatment, the cardiac output had returned to normal, and was 19 per cent less than the control cardiac output of the first catheterization, the arterial oxygen saturation had increased by 9 per cent, the plasma volume had returned to normal, while total blood volume and hematocrit were still elevated. The right ventricular and brachial artery pressures showed no change. It is of significance that between these two studies there was no demonstrable change in the cardiac silhouette (fig. 2). Between the second and third studies this patient was discharged from the hospital and remained ambulatory and free of failure on digitalis and diuretics. There was no significant change in the cardiac output, right ventricular end diastolic and brachial artery pressures, or peripheral resistance. The hematocrit had returned to normal although no phlebotomies had been done in this interval. The cardiac silhouette was smaller than on the first two roentgenograms (fig. 2).



a b c

FIG. 2.—Cont'd. Patient T.D.

Group III

Acute Digitalization. The third group consists of 2 patients without evidence of heart disease.

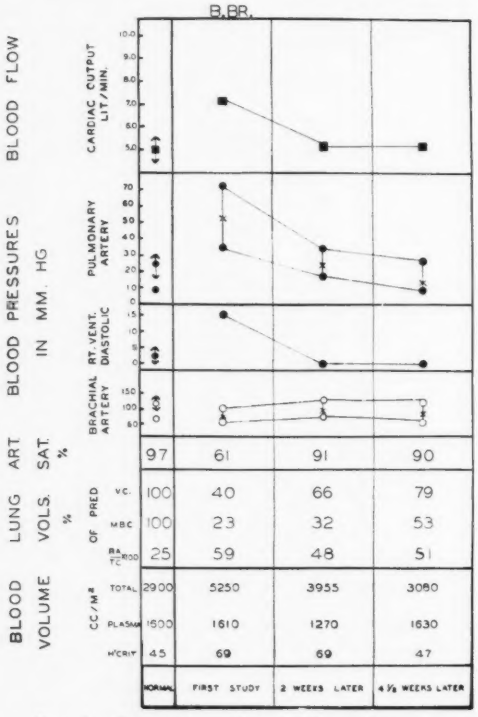


FIG. 3.—Comparison of serial hemodynamic and pulmonary function measurements in a patient (B.Br.) with chronic cor pulmonale. (For symbols, see figure 1. Art. Sat. % = per cent of arterial blood oxygen saturation; Lung Vols. = lung volumes; V.C. = Vital capacity in per cent of predicted value; M.B.C. = maximum breathing capacity in per cent of predicted value; $\frac{RA}{TC} \times 100$ = ratio of residual air to total lung capacity.)

The first study was done at the time of cardiac failure and before digitalization. The second and third studies were made two weeks and four and one-half weeks later, during the period of recovery from cardiac failure. Note that following recovery from failure (a) the cardiac output, pulmonary arterial and right ventricular pressures returned to normal, (b) the arterial blood oxygen saturation, vital capacity and maximum breathing capacity were greatly increased, and (c) the blood volume and hematocrit returned to normal.

The control cardiac outputs and stroke volumes of these 2 patients, listed in tables 6 and 7, were within normal limits. Both patients had pulmonary hypertension, although the pulmonary arterial systolic pressure of one (M. M.) was only at the upper limit of normal. The diastolic and mean pressures were elevated

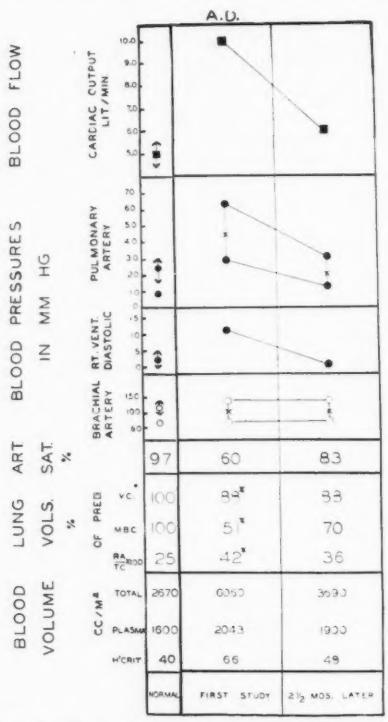


FIG. 4.—Comparison of serial hemodynamic and pulmonary function measurements in a patient (A.D.) with chronic cor pulmonale.

The first hemodynamic study was done at the time of cardiac failure. The first lung volumes, marked with an asterisk, were measured one week later and after digitalization. The second study, two and one-half months later, was done after complete recovery from cardiac failure. (For symbols, see figure 3.) The changes in hemodynamics and in pulmonary function were similar to those noted in figure 3. The blood volumes and hematocrit remained somewhat elevated.

The right ventricular end diastolic pressure of both patients was normal. The patient (M. M.) had brachial artery hypotension which had been repeatedly noted clinically. The brachial artery systolic pressure of the other patient (J. McC.) was elevated but the diastolic and mean pressures were normal. Peripheral re-

sistance was within normal limits. The total blood volume of both patients was somewhat increased with slight elevation of hematocrit in only one (J. McC.). The arterial oxygen saturation was only slightly reduced at rest, but it can be seen in table 1 that the saturation decreased considerably after exercise. The arterial oxygen capacity was within the limit expected from the hematocrit value.

After acute digitalization, one patient (M. M.) had a 12 per cent increase in cardiac output and stroke volume accompanied by a slight rise in pulmonary artery systolic pressure. The pulmonary artery diastolic and mean pressures and the right ventricular diastolic pressure showed no change. The brachial artery systolic pressure rose slightly but the peripheral resistance and heart rate remained constant. The other patient (J. McC.) exhibited no significant alterations in hemodynamics following digoxin.

Group IV

The 2 patients who make up the fourth and last group (tables 8 and 9) presented in this report differ from those of the previous three groups in that they have cardiac disease other than cor pulmonale, in addition to chronic lung disease. Both patients were in failure when first studied. Since the response to digoxin was different in the 2 cases, each will be discussed in detail.

In the first patient (J. P.) who had arteriosclerotic heart disease and tricuspid insufficiency (confirmed by auricular pressure curves) the control cardiac output and stroke volume were extremely low. The right ventricular systolic and diastolic pressures were considerably elevated. The pulmonary artery pressures were not measured. The blood pressures in the brachial artery were normal and there was a markedly increased peripheral resistance. An increased total blood and plasma volume was accompanied by a high hematocrit. The arterial oxygen saturation was somewhat reduced and arterial blood oxygen capacity was normal.

After digoxin the cardiac output increased by 21 per cent and this was accompanied by considerable rise in right ventricular and brachial artery systolic pressures. There was no change in right ventricular end diastolic or brachial artery diastolic and mean pressures or peripheral resistance. The heart rate decreased slightly.

The second patient (W. H.) (fig. 5) in this group had hypertensive and arteriosclerotic heart disease. The control cardiac output and stroke volume were reduced. Pulmonary hypertension

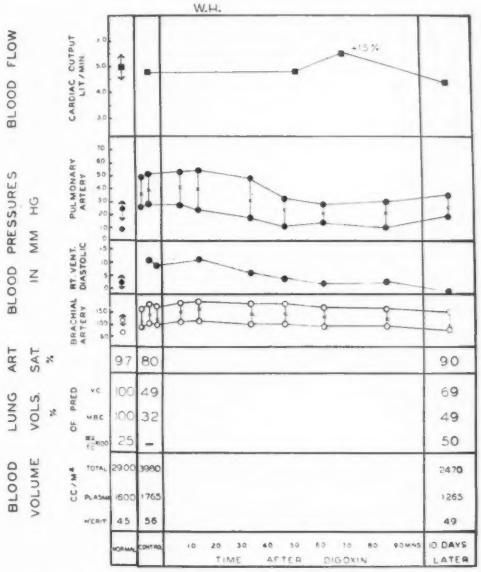


FIG. 5.—Acute effect of digoxin in congestive heart failure and comparison of the hemodynamic and pulmonary function measurements before and after recovery from congestive heart failure in a patient (W.H.) with hypertensive and arteriosclerotic heart disease and chronic pulmonary disease. (For symbols, see figure 3.)

Note that (a) acute digitalization was characterized by a rise in cardiac output and a fall to normal of both the pulmonary arterial and right ventricular pressures, and (b) that the cardiac output following recovery from failure was at the same level as noted in the predigitalization period.

and elevation of the right ventricular end diastolic pressure were associated with systemic arterial hypertension. Total blood and plasma volumes, as well as the hematocrit were well above normal limits. The arterial oxygen saturation was considerably decreased and the arterial oxygen capacity was normal.

After digoxin, a 15 per cent increase in cardiac output was associated with a marked reduction

in the pulmonary artery hypertension, while the right ventricular end diastolic pressure returned to normal. These changes were effected without alteration in arterial blood pressure, peripheral resistance or heart rate.

Ten days after the first study (tables 8, *B* and 9, *B*), during which time the patient had recovered completely from cardiac failure and had become ambulatory, the cardiac output had returned to approximately the same value as noted in the control period before digoxin was given. Mild pulmonary artery and systemic arterial hypertension persisted and the right ventricular end diastolic pressure was normal.

Discussion

In an attempt to evaluate the action of digoxin in these groups of patients, not only the immediate effects of the drug, but also some of the eventual readjustments in the circulation as a result of prolonged therapy have been investigated. Furthermore, the results of these studies have clarified to some extent the complex problem of cor pulmonale.

Acute Digitalization

The 5 patients with cor pulmonale in the first group had pulmonary hypertension and right heart failure, as evidenced by a markedly elevated right ventricular end diastolic pressure. Following digoxin the cardiac output rose and the filling pressure of the right ventricle and presumably the residual blood volume decreased, indicating better emptying of this chamber. Thus, as with patients in left ventricular failure, the drug apparently improved the function of the failing ventricle. These changes were accompanied by an increase in the pulmonary artery systolic pressure. Hence it appears that when an increase in blood flow takes place within a pulmonary vascular bed with a pathologically restricted capacity, this increased flow cannot be accommodated without a rise in pressure in the pulmonary artery.

In contrast to the patients with cor pulmonale and cardiac failure, all of those patients with cor pulmonale and no cardiac failure had no change in cardiac output, right heart or pulmonary artery pressures after digoxin. One of the 2 patients with pulmonary hypertension and no evidence of heart disease had no hemodynamic changes after the drug. However, both these patients had several of the same hemodynamic abnormalities found in the first group: pulmonary hypertension, hypervolemia, polycythemia and anoxia. In none of these patients was the right ventricular end diastolic pressure elevated or the cardiac output definitely abnormal. It would appear, therefore, that an increase in cardiac output is effected by digoxin only in the presence of cardiac insufficiency. This impression has been confirmed by the similar results obtained with digoxin in patients with heart disease of other etiologies who were not in cardiac failure.[6]

It is true that one case (M. M.) had a 12 per cent increase in cardiac output. This change may have been due to an effect of the drug for which there is as yet no adequate explanation. It is of interest that this man, who subsequently received no more digitalis, went into severe cardiac failure several months after this study. Hence it is possible that the myocardium may not have been normal even at the time of the drug study.

From the above results it appears evident that the response to digoxin in patients with cor pulmonale in failure resembles the reaction to the drug of patients with left ventricular failure.[1] Both groups respond with a rise in cardiac output, a reduction in filling pressure and better emptying of the failing ventricle. There were, however, certain differences in response between the two groups. In the 5 patients with cor pulmonale, the increase in cardiac output was not as large as was shown by the 5 patients in left ventricular failure. In the right ventricular failure group, the mean increase in cardiac output was 18 per cent with a range of 6 to 31 per cent, while in the patients with left ventricular failure the mean increase was 39 per cent with a range of 12 to 77 per cent. A number of factors may be responsible for this difference in cardiac output response to digoxin: inequality in muscle mass of the right and left heart, difference in pressure-volume relationship of the two ventricles, and difference in the characteristics of the vascular bed distal to each ventricle. From the data available it is

mpossible to state which of these factors were nvolved. Of considerably greater importance, nowever, is the fact that regardless of the quan- itative difference in cardiac output increase, in ach instance the filling pressure of the failing entricle returned to normal.

We may discuss further the fact that in the patients with cor pulmonale the increase in pulmonary flow following digoxin caused a temporary rise in pulmonary hypertension while in the patients with left ventricular failure, pulmonary artery pressures returned to normal. In the latter patients it is presumed that failure of the left heart resulted in an increase in residual blood volume in the left ventricle and auricle and hence produced an increase in pressure in the latter chamber which was reflected throughout the pulmonary vascular tree producing pulmonary hypertension. Thus, the acute reaction to digoxin serves to differentiate between pulmonary hypertension due to a restricted vascular bed and that due to failure of the left ventricle. This is illustrated by the response to digoxin in the 2 patients in the fourth group. One of these patients (J. P.) had a rise in right ventricular systolic pressure accompanying the rise in cardiac output, while in the other, all the pressures in the pulmonary artery decreased markedly. In the former, the acute response to digoxin indicates that a restriction in the pulmonary vascular bed is the predominant cause of increased pulmonary artery pressures, while in the latter the acute response points to left ventricular failure as the primary cause of pulmonary hypertension.

Mode of action of digoxin. In a previous report,[1] evidence for a predominantly myocardial effect of digoxin was presented. However, no conclusive evidence for such an effect of the drug could be found in the data of the 5 patients with cor pulmonale in failure, since the cardiac output increase was always accompanied by a fall in the right ventricular end diastolic pressure. This fall, which of necessity would be accompanied by a fall in venous pressure, could result from venodilatation or a direct myocardial action of the drug. In the former instance, there would be a reduction in the venous return and in the latter, as a consequence of better emptying of the right ventricle, there would be a reduction in ventricular residual blood volume and filling pressure and a fall in venous pressure. Evidence to support the latter concept is found in the reaction to digoxin in the patient (J. P., table 8) with tricupsid insufficiency who showed an increase in cardiac output without change in the markedly elevated right ventricular end diastolic pressure. This response to digoxin in the presence of tricuspid insufficiency has been noted in other patients in congestive failure with heart disease of other etiologies.[6] In the absence of a fall in right ventricular filling pressure and by inference an absence of a fall in venous pressure, a venodilator action of digoxin is not likely. Dilatation of the pulmonary vascular bed and a fall in pulmonary vascular resistance might be considered as a possible cause for the increased cardiac output, but this is unlikely in view of the rise in pulmonary artery pressure.

Since the venous action of digoxin, as suggested by McMichael,[7] was not substantiated by the studies in patients with left ventricular failure[1] and patients with tricuspid insufficiency, it would appear more reasonable to postulate a drug action that is uniform in all patients with cardiac failure. The concept that the primary action of digoxin is upon the myocardium permits adequate explanation of the effects of the drug in all types of failure. Despite the fact that there is no conclusive evidence in the data here presented which disproves the theory of the venous action of digoxin, it is difficult to believe that the mode of action varied from one group of patients to another, e.g., a venous action in right sided failure and a myocardial action in left ventricular failure. The response of the circulation to a primary myocardial action of digoxin, however, may vary from one group of patients to another depending upon the physiological abnormalities present. Since there was no consistent effect on heart rate, it is apparent that the myocardial action is at least in some cases independent of change in rate.

As can be seen from the results in this report as well as those previously published,[1] the effect of digoxin upon the peripheral arteriolar bed is variable. These data suggest that changes in peripheral vascular resistance after digoxin represent a balance between a primary vaso-

constrictor effect upon the arterioles and reflex alterations secondary to changes in stroke volume.

With a primary myocardial action of digoxin resulting in an increase in cardiac output and a decrease in right heart filling and peripheral venous pressures, one must assume some redistribution of blood since presumably the total blood volume remains unchanged during the acute experiment. If the venous system was nearing the limit of its distensibility a large decrease in venous pressure could occur with only a small volume shift of blood from the venous system into another part of the circulation, for instance the pulmonary vascular bed. However, if venous distention were not near its limit, a large fall in venous pressure could only occur as a result of either a large shift of blood out of some part of the venous bed or with an increase in capacity of this bed. As it is unlikely that a large volume of blood could be accomodated in the systemic arterial or capillary bed, the site of the redistribution could only be the pulmonary vascular bed and/or some part of the systemic venous system (liver, splanchnic area, etc.). The mechanism of venodilation, if it occurs, may be of reflex origin or possibly related to the increase in venous oxygen tension or to the action of digoxin. Whether this mechanism is present or not, the myocardial action of digoxin remains the dominant factor.

It should be emphasized that all the hemodynamic changes produced by digoxin here noted were only followed for a period of one and one-half to two hours. These acute changes do not necessarily reflect the final or optimal effect of the medication and any conclusions as to the long term results of digoxin are not justified.

Long term results of therapy. The striking clinical improvement in the patients with cor pulmonale after recovery from failure prompted re-examination of their cardiopulmonary function.

Respiratory studies revealed more efficient pulmonary function and there was a marked increase in the arterial oxygen saturation in every patient. The profound anoxia demonstrated by these patients with chronic pulmonary disease at the time of their first studies, and manifest clinically as cyanosis, may have resulted from perfusion by venous blood of poorly ventilated alveoli, from disturbance of oxygen transfer across the alveolar-capillary membrane, or from a reduction in the area of the capillary-alveolar interface, or a combination of all three. However, some studies, to be reported separately,[8] indicate that in these patients, in addition to a reduction in area of capillary-alveolar interface, there was a large proportion of alveoli low in oxygen as a result of hypoventilation, and therefore the venous blood perfusing these areas reached the pulmonary veins inadequately oxygenated, thus making the venous admixture in the arterial blood larger than normal. Following therapy, as a result of more adequate over-all alveolar ventilation, a much smaller amount of venous blood was inadequately oxygenated and, therefore, there was an increase in arterial oxygen saturation.

The readjustments of the circulation after the patients had recovered from cardiac failure were surprising. The mechanisms whereby these readjustments took place cannot be stated with certainty but can at least be speculated upon.

The decrease in cardiac output noted in all the patients following restoration of compensation may have been a result of a change in the fundamental physiological properties of the heart muscle. A schematic representation of the sequence of events is attempted in the diagram in figure 6. When the patients were in congestive failure, presumably the optimal end diastolic stretch of the muscle fibers had been exceeded (position 1 in figure 6). This resulted in a large dilated heart and large residual diastolic blood volume. The immediate effect of digoxin was to increase systolic ejection and to decrease residual volume and ventricular filling pressure (position 2 in figure 6). As the heart and circulation continued to improve the ventricle would ultimately be more completely emptied of the excessive residual blood, there would be a reduction in the diastolic heart size and a shortening of the initial end diastolic length of the myocardial fibers. In accordance with physiologic principles, this would result in a smaller cardiac output as found in the second

studies on these patients (position 3 in figure 6). Changes in blood volume may have played a role in the circulatory readjustments since the patients (A. D. and B. Br.) with the greatest reduction in circulating blood volume also had the largest reduction in cardiac output. That the decrease in cardiac output cannot be ascribed entirely to a decrease in blood volume is obvious since the latter was not a constant finding.

In those patients in whom the blood volume was reduced after prolonged therapy, there was apparently a much greater loss of red blood cells than of plasma. This red cell loss might be attributed to (a) a decrease in the probable stimulus (anoxia) for red cell production, (b) an increase in destruction of presumably abnormal red cells, or (c) an error in the computation of the red cell volume, since it is known that the hematocrit in the presence of polycythemia is difficult to measure precisely.

The most unexpected finding in the circulatory readjustments after recovery from failure was the marked reduction in pulmonary arterial hypertension. It had long been tacitly understood that the anatomic lesions induced by certain types of chronic lung disease, produce irreversible pulmonary hypertension. Since the latter was found to be reversible in this group of patients, it is apparent that besides the basic anatomic alterations of the pulmonary vascular bed other factors must be considered as causes of pulmonary hypertension.

Of probably the greatest importance in the production of pulmonary hypertension is the relationship between pulmonary blood flow and the capacity of the pulmonary vascular bed. With a normal vascular bed which is readily distensible it is possible to increase the pulmonary blood flow three-fold without augmenting the pulmonary artery pressure.[9,10] Once pathologic changes, either anatomic or physiologic, have reduced the capacity and distensibility of the vascular bed, the normal relationship of flow to capacity is distorted and the pulmonary artery pressure may rise with an increase in blood flow.[11] Pulmonary hypertension, then, depends upon the balance between the degree of restriction of the vascular bed on the one hand, and the amount of blood flow through this bed on the other. In the presence of only a mild or moderately curtailed vascular capacity pulmonary hypertension may not result until the blood flow is increased two-fold (e.g., A. D., tables 2 and 3). In some patients with a severely curtailed vascular bed, hypertension may persist at rest, even with a slightly elevated or normal blood flow. This concept suggests that the patients with the least degree of pulmonary vascular encroachment may have the highest cardiac output. Conversely, a reduction in cardiac output and hence in pulmonary blood flow, after restoration of cardiac compensation might cause reduction in pulmonary artery pressures.

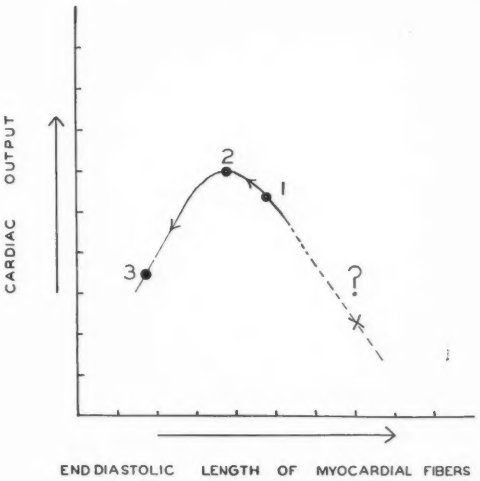


FIG. 6.—Schematic curve relating changes in cardiac output and changes in myocardial fiber length at the end of diastole in chronic cor pulmonale.

Direction of arrows indicates increasing values. For discussion, see text.

It is known that acute anoxia produces pulmonary hypertension even in normal subjects.[12] It is, therefore, not unlikely that severe degrees of chronic anoxia may increase pulmonary artery pressures and hence an increase in arterial oxygen saturation may result in a reduction in pulmonary hypertension.

Increased blood viscosity as a result of polycythemia may also play a part in the production of pulmonary hypertension by increasing resistance to flow, although polycythemia is not a constant finding in chronic cor pulmonale.

That restoration to a normal red cell volume may be an important factor in the alleviation of the pulmonary hypertension is suggested in the third study of one patient (B. Br., tables 2 and 3) where a drop in hematocrit, as a result of phlebotomies, was accompanied by a fall to normal of the somewhat elevated pulmonary artery pressures.

It is, of course, well known that pulmonary hypertension may result from left ventricular failure. That this factor was not operative in these patients with cor pulmonale is demonstrated by their acute response to digoxin: the pulmonary artery pressure rose as the cardiac output increased, while in patients with left ventricular failure pulmonary hypertension was relieved.[1] The patient W. H. (tables 8 and 9) is a good example of the differentiation of these two types of hypertension since, in spite of severe pulmonary disease with anoxia, polycythemia and hypervolemia, the pulmonary artery pressures fell sharply after acute digitalization. The fact that these pressures remained at the upper limit of normal after prolonged therapy may indicate the persistence of mild left ventricular failure.

A Tentative Concept of Chronic Cor Pulmonale

The data presented in this paper, showing the reversible character of some of the changes present in chronic cor pulmonale have delineated to some extent the sequence of events in the production of this form of heart disease and in the development and alleviation of cardiac failure in such patients.

From these studies it appears that the following physiological findings occur to a greater or lesser degree in patients with chronic cor pulmonale: anoxia, polycythemia, hypervolemia, normal or high cardiac output, and pulmonary hypertension. Tentative concepts as to the interrelation of these factors in the production of cor pulmonale will be discussed. (For a simple schema, see figure 7.)

As a consequence of the underlying pulmonary disease, respiratory function may be so altered as to result in anoxia. The latter condition of itself may effect an increase in cardiac output. Anoxia may also be the initiating factor in the production of polycythemia and hypervolemia. However, it is well known that many patients with chronic pulmonary disease and anoxia do not have polycythemia. It may be that long term studies of these patients will reveal that the duration and degree of anoxia are important in the production of this secondary polycythemia. Regardless of the exact mechanism involved in the production of polycythemia and hypervolemia, the latter may effect an increased diastolic right ventricular volume and thereby produce an increased stroke volume and cardiac output. The ventric-

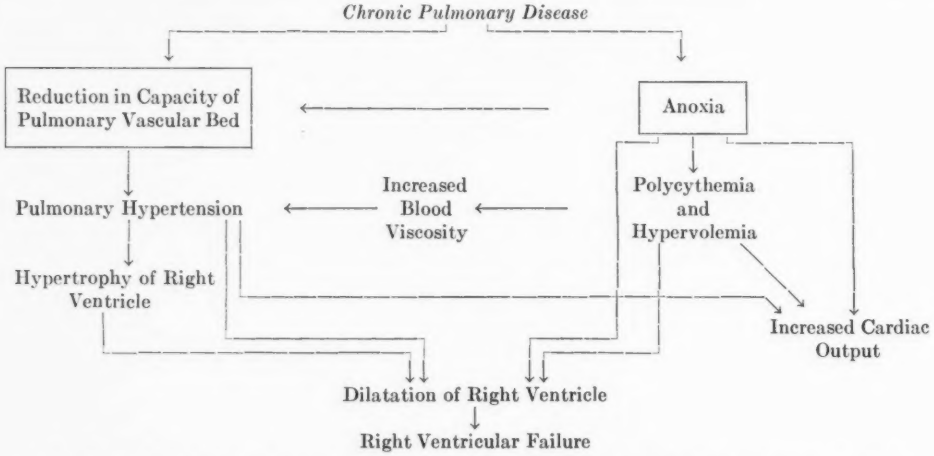


FIG. 7.—Comprehensive schema of interrelated factors in the production of chronic cor pulmonale.

ular muscle can maintain this increased output provided that the optimum value for the end diastolic stretch is not exceeded. Obviously with the rising output of the right ventricle, there is an increasing venous return to the left ventricle and, in turn, its stroke volume also increases. Possibly other factors, as yet unknown, may act to increase the cardiac output. In this regard it has been suggested that the increased blood flow and polycythemia are homeostatic responses directed towards the satisfaction of tissue oxygen needs in the presence of anoxia.

In this series of patients with chronic cor pulmonale in failure, information is available concerning some aspects of the problem of gas exchange in the tissues, i.e., oxygen transport, oxygen utilization, and oxygen tension in the arterial and mixed venous blood. From the data in table 10 it can be seen that the oxygen transport and oxygen utilization in 2 of the 5 patients (A. D. and B. Br.) were within normal limits, while in the other 3 patients, during the period of heart failure, oxygen transport was low and oxygen utilization increased. In all, however, the oxygen tensions in the arterial and mixed venous blood were markedly reduced and bore no apparent relationship to oxygen transport or utilization. Even in the 2 patients where an increase in cardiac output and polycythemia appeared sufficient to maintain normal oxygen transport and utilization, arterial and mixed venous blood oxygen tensions were reduced. Furthermore, following recovery from failure, only one patient had an increase in oxygen transport and a reduction in oxygen utilization which occurred concomitantly with a reduction in cardiac output and in polycythemia. It can also be seen that as these patients recovered from failure, the oxygen tensions in the arterial and mixed venous blood rose and presumably favored oxygen exchange in the tissues. Again this improvement occurred with a reduction in cardiac output and polycythemia.

However, since there is no information available concerning the proportion of total blood flow directed to different viscera and the optimal tension at which oxygen is utilized by the parenchyma of each organ, the problem as to whether or not the tissue needs of the various organs are satisfied cannot at present be solved.

Another consequence of the chronic pulmonary disease is alteration of the pulmonary vascular bed which may be upon an anatomic or physiologic basis, or both. The exact changes are not as yet clearly defined but may include a reduction in the area of the bed, a reduction in the caliber of the vessels themselves or a decrease in the distensibility of the vessels. The resultant restriction of the pulmonary vascular bed may be extensive enough to produce hypertension at rest because of the distortion of the normal pulmonary flow-capacity ratio. However, it is apparent from the studies presented in this report that the anatomic lesions, which are presumably not reversible, cannot be the sole factor in the production of pulmonary hypertension since the latter was reversible. It would appear that in some cases at least, physiologic alterations must be superimposed upon the anatomic lesions before hypertension

TABLE 10.—*Data on Oxygen Transport, Utilization, and Tension in Five Patients with Chronic Cor Pulmonale (a) in Cardiac Failure and (b) After Recovery*

Case		Oxygen transport* (cc/Min.)	Oxygen utilization† in %	Blood oxygen tension (mm. Hg)	
				Art.	M.V.B.
Normal		1050	20–25	96	38
A.D.	(a)	1230	23	37	26
	(b)	906	25	46	33
B.Br.	(a)	907	28	34	26
	(b)	850	25	62	35
J.B.	(a)	556	46	28	19
	(b)	892	26	48	32
B.Bu.	(a)	657	36	42	27
	(b)	642	33	43	31
T.A.	(a)	557	39	46	24
	(b)	571	32	69	34

* Oxygen transport = Arterial blood oxygen content × Cardiac output.

† Oxygen utilization = Oxygen consumption/Oxygen transport.

Art. = Arterial; M.V.B. = Mixed venous blood.

is produced. Anoxia, by affecting vasomotor tone of the lung vessels and thereby further reducing the capacity of the pulmonary bed, polycythemia by increasing blood viscosity and hence increasing resistance to flow, may precipitate or aggravate pulmonary hypertension even in the presence of a normal blood flow. Any increase in the pulmonary blood flow in the presence of a restricted vascular bed would of itself produce pulmonary hypertension.[9–11] Many of the patients with chronic cor pulmonale have increased blood flow even at rest which, in addition to all of the other factors previously mentioned, would aggravate pulmonary hypertension. The possible presence of an anastomosis between bronchiolar and pulmonary arterioles must also be considered as a possible factor in the production of pulmonary artery hypertension.[13]

Hypertrophy of the right ventricle may ultimately result from pulmonary hypertension. It is at this stage that the first clinically demonstrable involvement of the heart occurs and the disease is classified as chronic cor pulmonale.

When the right ventricle can no longer cope with the increased amount of work required of it, dilatation and eventual failure of this chamber result. It is an essential part of this concept that dynamically the left ventricle, which has not been subjected to work against an increased resistance, remains normal and therefore is still able to empty itself efficiently in the presence of an increased venous return. In some cases a sudden and marked increase in anoxia, presumably by a direct effect upon the strained right ventricular myocardium, may precipitate cardiac dilatation and failure. The element of hypervolemia may also play a role in the production of failure. The increasing blood volume may have so added to the diastolic volume of the right ventricle that the optimum diastolic stretch of the muscle fibers has been exceeded and, therefore, its efficient emptying is impaired, residual diastolic blood volume increases, diastolic pressure rises and failure ensues. It should be noted that the hypervolemia of itself is not the primary cause of congestion of the peripheral venous bed[14] since the fall in venous pressure accompanying the increase in cardiac output after digoxin took place before there could have been any appreciable reduction in the large circulating blood volume.

Since it was shown that the failing heart in cor pulmonale increased its output and lowered its filling pressure in response to digoxin (position 1 to 2 in figure 6), it seems most likely that, reversing the sequence of events, when the heart goes into failure the cardiac output is lowered from its previously high level but still may be higher than normal. The paradox of a high cardiac output in the presence of failure can be explained by the fact that in chronic cor pulmonale the ventricular fibers are relatively intact as compared to those in patients with intrinsic myocardial damage such as is found in coronary artery disease, rheumatic myocarditis, etc. The ventricles are therefore able to sustain a high cardiac output not only before failure ensues but even in its presence. Thus can be seen the mechanism whereby in chronic cor pulmonale, cardiac failure may occur in the presence of a high cardiac output. It is possible that patients with cor pulmonale in failure at the end stage of their disease when the myocardium is greatly impaired may have cardiac outputs even lower than normal (point X in figure 6).

In the analysis of the various factors operating in the production of chronic cor pulmonale, no attempt has been made to define the relative importance of any one mechanism. It is obvious that these mechanisms are all interrelated and the importance of each may vary from patient to patient. In the matter, for example, of the production of cardiac failure, the evolution may be gradual and progressive as a result of prolonged and sustained pulmonary hypertension or may be acute as a result of a sudden increase in anoxia secondary to bronchiolar obstruction associated with respiratory infections. It has been frequentlynoted that patients with cor pulmonale will go rapidly into cardiac failure with infections which do not involve the respiratory tract. It may well be that the increased cardiac output generally associated with hyperthermia is sufficient to increase pulmonary hypertension acutely to such a degree that the right ventricle fails.

Clinically, the most important fact demon-

strated by these investigations is that the vicious cycle constituting the whole picture of chronic cor pulmonale in failure can be interrupted and altered by therapy. Therapy should therefore be directed at the reversible features in the cycle. Respiratory function can be improved and anoxia alleviated by a variety of measures, especially those relieving bronchospasm and reducing bronchial secretions. Oxygen therapy, particularly in acute anoxia, is beneficial since it may correct one of the basic physiologic abnormalities in these patients. However, many of the patients with cor pulmonale have longstanding high blood carbon dioxide content due to alveolar hypoventilation. Presumably in such patients the respiratory centers no longer respond to an increase in carbon dioxide and depend upon oxygen lack for the regulation of respiration. If oxygen is administered *continuously* or in high concentrations to these patients, the oxygen lack is removed as a stimulus to respiration, hypoventilation becomes more marked, carbon dioxide tension in the blood increases still further and narcosis results.[5, 15, 16] For these reasons, the intermittent use of oxygen is the safest method of administration in the presence of a high blood carbon dioxide content. With the subsidence of the acute episode oxygen therapy should gradually be withdrawn.

Improvement of the cardiocirculatory function can be obtained by digitalization and by reduction of the total circulating blood volume by means of phlebotomies and mercurial diuretics. Decision as to the amount of blood removed should in the main, rest upon determinations of the hematocrit as the hemoglobin content may be misleading in these patients.

Summary and Conclusions

1. The early effects of intravenous digoxin were studied by the cardiac catheterization procedure in 5 patients with chronic cor pulmonale in right-sided failure.

2. Digoxin produced a rise in cardiac output, a reduction in filling pressure and presumably a better emptying of the failing ventricle in these patients. The increase in blood flow through a restricted pulmonary vascular bed was accompanied by a rise in pressure in the pulmonary artery.

3. The striking clinical improvement in these 5 patients after recovery from cardiac failure was accompanied not only by more efficient pulmonary function, as shown especially by a marked increase in arterial oxygen saturation, but also by remarkable circulatory readjustments. The cardiac output had decreased considerably as compared to the value obtained at the time of cardiac failure and the pulmonary arterial pressures were almost normal.

4. The reversibility of the pulmonary hypertension in these patients with chronic cor pulmonale suggests that, in addition to anatomic alterations of the pulmonary vascular bed, certain physiologic abnormalities such as anoxia, polycythemia and distortion of the normal relationship of blood flow to vascular capacity may be important factors in the production of pulmonary hypertension.

5. The effects of acute digitalization were observed in 3 patients with chronic cor pulmonale who were not in cardiac failure, and in 2 patients with pulmonary hypertension and no evidence of cardiac disease. In none of these patints was there any appreciable change in cardiac output or right heart pressures.

6. A study was also made of the acute response to digoxin of 2 patients in cardiac failure who had both chronic pulmonary disease and heart disease of etiologies other than cor pulmonale. In these 2 cases, both of whom had pulmonary hypertension, a fall in pulmonary artery pressure following digoxin served to differentiate pulmonary hypertension due to left ventricular failure from that due to a restriction of the pulmonary vascular bed.

7. A tentative concept of some of the mechanisms involved in the production of chronic cor pulmonale is presented and discussed.

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Life Stress and Cardiovascular Disorders

By HAROLD G. WOLFF, M.D.

An amassing body of data demonstrates further the growing importance to medicine of the recognition that, for man, reactions to threats in the form of symbols, especially when sustained, may be more important than response to assaults. Certainly, many aspects of cardiovascular disease may be looked upon as functions of man's goals, his methods of achieving them, and the conflicts they engender. In this paper the importance of life stress to the cardiovascular system in various conditions is discussed; case examples demonstrate the relationship between stressful situations and circulatory efficiency, faulty exercise tolerance in patients with or without structural heart disease, the hypodynamic response, cardiac arrhythmias, electrocardiogram, blood pressure, hypertension and renal blood flow.

THE NATURE OF STRESS FOR MAN

THE STRESSES to which man is exposed include assaults by many living forms that aim to invade as parasites or to destroy; by meteorologic and climatic crises that pass sometimes predictably and often whimsically over the earth's surface; by mechanical, electrical and thermal forces that operate upon man merely in terms of his structure, mass and volume; and by elements of the earth's crust which man often dangerously manipulates for his comfort and delight or to fulfill his passion for destruction.

But constituted as he is, man is further vulnerable because he reacts not only to the actual existence of danger but to threats and symbols of assaults experienced in his past. These call forth reactions little different from those to the assault itself. Also, since he is a tribal or group creature, he depends for his very existence upon the aid, support and encouragement of other men.

Indeed, he lives his life so much in contact with men and in such concern about their expectations of him that perhaps to him the greatest threat of all is his doubt about his ability to live the life of a man. He is threatened by those very forces in society upon which he is dependent for nourishment and life. He must be part of the tribe and yet he is driven to fulfill his own proclivities. When these goals are divergent, conflict arises which causes him to be pulled two ways at the same time and threatens his security. These threats and conflicts are ubiquitous, and constitute a large section of the stress to which man is exposed.

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RECOGNITION OF THE RELATION BETWEEN LIFE STRESS AND THE FUNCTIONS OF THE HEART

The action of, and sensations about the heart have long been linked with man's fears and loves. Our language is replete with examples indicating this ancient coupling, and indeed, the word "heart" has itself become a symbol of the human spirit. Widely used to imply courage or its lack are such phrases as: to hearten, or dishearten; to put the heart into, or inversely, to take the heart out of; lion-hearted, big-hearted, warm-hearted, soft-hearted, tender-hearted, or, on the other hand, cold-hearted, steel-hearted, hard-hearted, heavy-hearted and heart-sinking fear. The index of Barlett's "Familiar Quotations" composed of columns of key words contains more than nine columns of the word heart, a frequency of occurrence exceeded only by such words as man, life and love. In the index of Roget's "Theasaurus," the word heart outnumbers all others.

Legend and folklore abound in references to the heart's action as expressive of the man. Thus, in the ancient Parsifal legend modified by Wagner, Amphortas the inadequate son of a strong-leading father receives a never-healing wound in his heart by the spear of life and passion during a brief attempt to demonstrate his power. He is turned into a couch-ridden

invalid who sinks in faintness and pain whenever he attempts, in the pattern of his father, to assume the imposed responsibilities of his high office. It is implied that he is ultimately "cured" when his wound is touched by the spear now in Parsifal's hand and he is relieved of his responsibilities.

Thesis

The cardiovascular apparatus may be looked upon as a device essential to the maintenance of homeostasis. It serves to secure body economy by maintaining an equilibrium of opposing forces. This it achieves by a series of adaptive and protective reactions. Many of these reactions evoked by assaults or threats are operated at great cost to the organism, a matter of small moment except for transient symptoms if the parts are strong and the stress of short duration. But should the adaptive and protective patterns be maintained unduly long or the reacting organs be weak, or already operating under strain, or should the protective reactions exert an additive effect with other stresses, then the system may collapse.

Obviously, an equipment such as the cardiovascular apparatus that controls the distribution of body fluids is basic to any reaction, and to isolate reactions is arbitrary. But for didactic purposes there will be selected for consideration and as examples of a process, a few patterns involving conspicuous changes.

Life Stress and Circulatory Efficiency

Some years ago my associate, Dr. George Wolf,[1, 2] made measurements, before and after exercise, of the pulse, blood pressure, the ventilatory index (the amount of oxygen utilized in terms of the amount of air breathed in), cardiac output, and stroke volume. He found, for example, that a healthy individual who was asked to do a task he did not relish, a task at which he was convinced he would fail, exhibited in response to the standard exercise test a striking increase in blood pressure and stroke volume, and a decrease in ventilatory efficiency. This augmented response to a standard test persisted for forty-eight hours after the task in question did turn out to be (in his eyes) a complete failure. Changes of similar nature and duration were noted to be linked with anger and tension. Such responses are referred to as hyperdynamic reactions to stress.

During periods of domestic difficulty for example, healthy subjects exhibited physiologic inefficiency or inability to return promptly to the initial resting state after a standard exercise. Similar impairment of the subject's ability to return to previous levels was observed after a night in which the subject had only three hours of sleep. Also, healthy subjects reacted with similar decreases in circulatory efficiency to the assault of a minor infection and to the emotional assault of an implication of inadequacy.

It was inferred, in short, that the heart of the healthy, relaxed subject responds to the standard exercise situation with increases in stroke volume and output, which two minutes later return to the initial resting state. When the same individual is under stress the performance of his heart while at rest may be unaltered and may respond to exercise in the usual adequate fashion. But quite often after exercise his heart continues to behave as though he were still doing extra work and only slowly returns to the resting level of performance. It was suggested that under these conditions an organ made fragile by disease might suffer serious impairment of function.

Some patients with precordial symptoms in situations of stress are morbidly interested in their heart which they feel is functioning in a peculiar way. Actually, as was demonstrated by Dr. George Wolf,[1, 2] the hearts of many individuals during periods of duress may function differently, in that there is an increase in the cardiac output and the force of contractions, and arrhythmias as well, all of which may give rise to unusual chest sensations.

Also, dyspnea is often an accompaniment of stress. X-ray studies by Dr. Stewart Wolf[3] demonstrate a difference in the action of the diaphragm during a period of emotional turmoil. During this time of stress the diaphragm is flattened, due to increased muscular contraction and shortening. This phenomenon may be responsible for such symptoms as inability to draw a full breath, a substernal tightness or cramp, and a sensation of breathing only with

the top of the chest. An additional factor was demonstrated in a young woman with nocturnal dyspnea. In this patient the stress of unexpressed anger and hostility caused an exaggerated pressor response, hyperventilation and decreased ventilatory efficiency. An interview which brought these feelings to the surface caused a circulatory and ventilatory response similar to that produced by strenuous muscular work. These were the basis for the nocturnal dyspnea. The patient's nocturnal dyspnea diminished after she was given an opportunity freely to discuss these feelings.

Thus, with such dyspnea, not only are the rate, depth and muscular pattern of respiration appreciably modified but also the rhythm is disorganized. Thus, slow, deep, sighing respiration alternates with apnea and rapid, shallow, ineffective movements.

Substernal and precordial pain and discomfort results not only from reduced myocardial circulation but also from sustained contractions of the diaphragm, as mentioned above, and the sustained and forceful contraction of the intercostal, pectoral and shoulder muscles. Such sustained contractions of skeletal muscles is a common accompaniment of prolonged emotional tension and conflict in both those with and without structural defects of the heart.

As an outgrowth of these earlier studies by Dr. George Wolf, emphasis was placed upon the reactions to persistent low-grade stresses and strains which are a part of "every day" living and which constitute the core of the bedside problem, rather than upon the well-known responses to major life crises. It was possible to infer that many of the symptoms associated with cardiovascular disorders are not directly attributable to structural defects but to alterations in function representing reactions to life stress. Thus, in response to stress-producing life situations in association with anxiety, anger, guilt, rage, frustration and tension, dyspnea associated with inefficient pulmonary ventilation may occur. And in similar stress situations in the presence of anatomic narrowing of the coronary arteries, heart pain may result from increased work of the heart attendant upon prolonged elevation of the blood pressure and cardiac output. On the other hand, as will be considered later as part of the hypodynamic reaction to stress, heart pain may also result from a fall in the cardiac output and coronary blood flow in association with feelings of desperation and defeat.

Faulty Exercise Tolerance in a Setting of Tension, Anxiety and Neurocirculatory Asthenia

A careful analysis of the feeling states and circulatory changes of neurocirculatory asthenia has more recently been undertaken by my associates Drs. Ian Stevenson, Charles Duncan and Stewart Wolf.[4] The close relation between symptoms and various life situations was exemplified by several patients. Thus, a 24 year old housewife felt deep resentment about an ailing mother. The daughter's symptoms were palpitation, faintness, dyspnea, and headache. Over a period of six months she had fourteen interviews, during which her pulse rate was taken before and two minutes after the standard exercise. There was gradual improvement until finally her exercise tolerance was normal, and she was without complaint. However, in a setting of insecurity at work she had an exacerbation of symptoms.

Exercise tolerance was ascertained in a 32 year old housewife, in a setting of anxiety and the manifestations of neurocirculatory asthenia. She had a dominating, perfectionistic husband who interfered with her endeavor to bring up their child. Palpitation and dyspnea temporarily dwindled after full verbal expression of resentment towards her husband. Her heart rate was slower and stroke volume was increased. During subsequent interviews she expressed further resentment toward her husband's attitude of indifference which made her feel unneeded or menial. Four months later, after fifteen such therapeutic visits, the tests showed further improvement in circulatory efficiency and the patient then remained symptom free.

A 38 year old female with neurocirculatory asthenia was observed for several months. She had been married but had been abandoned by her husband eight years before. Also, she had had Graves' disease five years before. Her symptoms during the period of study were palpitations following exertion and after meals

which made her afraid to eat. In a setting of anxiety, with symptoms when the heart rate was high and stroke volume decreased, after ten minutes of relaxation following the expression of her resentment she showed increased stroke volume with a decline in heart rate, indicating increased circulatory efficiency. She was then free of symptoms.

A striking example of the nonfixity of the effort syndrome is afforded by a patient described by L. F. Bishop.[5] The patient, a farmer, was examined under Army auspices on the occasions of his being called to military duty during both World War I and II. Although an interval of 25 years separated the two examinations, the findings were essentially the same. The patient was incapacitated by circulatory and ventilatory dysfunction as well as by accompanying anxiety. Yet it was clear that he functioned otherwise in the interval between wars. Shortly after his discharge during World War I and in the 25 year interval, he worked hard and long in the development and cultivation of a productive farm, and, apparently, was capable of doing sustained hard work. It must be inferred that the circulatory inefficiency precipitated by army life, was temporary and reversible, and the occurrence of defects was dependent upon special circumstances of stress, and not on stress in general.

The circulatory dynamics, before, and two, three, five, and ten minutes after a standard exercise test (Master) were studied in three groups of subjects by Dr. Stevenson and coworkers.[4] The first group included healthy subjects who by their own statements and behavior appeared to be optimally relaxed at the time. The second group consisted of healthy subjects who were unable to relax completely because of preoccupation or mild tension associated with their immediate personal problems. The third group was comprised of patients with overtly manifest anxiety, including those with neurocirculatory asthenia. The increment of cardiac output in preoccupied healthy persons (second group) compared to relaxed healthy subjects (first group) was largely achieved by increases in stroke volume. The increment of cardiac output in patients with sustained and overt anxiety (third group) compared to those preoccupied (second group) was largely achieved through increases in heart rate. The response of patients with anxiety is an increment of cardiac output largely composed of increase in heart rate as compared with other groups, with less resting time and therefore with less output per beat. Thus, both are operating uneconomically but in somewhat different fashion.

Along with these changes in feeling state and circulatory effects during periods of sustained stress are changes in the regulation of body temperature. Thus Graham, Goodell and Wolff[6] at the New York Hospital have been able to show that the amount and duration of elevation in body temperature in response to a given amount of work done is closely related to the pre-existing feeling state. In general, during periods of sustained emotional tension and conflict a given amount of work produced a greater rise of body temperature and for a longer time than did similar work done during a period of relative tranquility. This observation gains interest in light of the observations of Meyer Friedman[7] who calls attention to the fact that patients with functional heart disease often exhibit hyperthermia with temperature elevations of 1 to 2 degrees F. Moreover, in a few suggestive experiments he has shown that such patients in response to given amounts of typhoid vaccine given intravenously elevated their body temperatures approximately 4 degrees F., in contrast to a group of more relaxed persons in whom the elevation was about 1 degree F.

Variations in Exercise Tolerance in Patients with Structural Heart Disease

Output studies on a 22 year old female with patent ductus arteriosus (angiographic studies) were made during periods of initial anxiety which gradually diminished over a period of months by Dr. Stevenson and co-workers.[4] At the outset this patient had complaints of palpitation, dyspnea and weakness, and muscle aching. Dancing, her favorite recreation, was impossible, and fatiguability striking. Symptoms were precipated by recent conflicts. Approximately six to eight visits brought relaxation and reassurance about the nature of

the heart lesion, as well as frank expression of sexual guilt feelings. Also, there concurrently occurred improvement in her life situation and better living conditions. Although symptoms were almost gone and exercise tolerance was greatly improved, the latter was still below average for the healthy subject.

A 34 year old female with aortic insufficiency, mitral stenosis and rheumatic heart disease was studied. Anxiety and effort syndrome were apparent. The heart was enlarged but well compensated. She complained especially of palpitation, and effort intolerance. The patient's anxiety was heightened by a gloomy prognosis of complete invalidism at age 42 ("in a wheel chair at 42"). Pulse rate was taken two, four, and seven minutes after standard exercise during a period of anxiety and was found to be rapid with many extrasystoles. Taken again after ten minutes of relaxation, it was still more irregular. One year later, after twenty therapeutic interviews, her pulse rate was slower and regular and exercise tolerance was much improved. The patient was without complaints.

The Hypodynamic Response

Although the hyperdynamic response during stress seemed much more common, a hypodynamic reaction was also elicited. Such a hypodynamic reaction for example was demonstrated in a healthy subject who felt "let down" and "betrayed" by the group with which he identified himself. His response to exercise was an actual drop in the cardiac output and blood pressure to levels below that of the initial or resting state.

A young male with complaints of precordial pain felt caught in a situation from which there was no escape, and had, when discussing his situation, a fall in cardiac output, and a slight increase in blood pressure associated with electrocardiographic changes and precordial pain. It was postulated in this individual that the hypodynamic reaction resulted in a decreased coronary circulation and relative myocardial anoxia with resultant pain.

Cerebral anoxia attendant upon diminished venous return to the heart may give rise to feelings of giddiness and faintness. But the latter feelings may also result from hyperventilation, which is followed by cerebral vasoconstriction, impaired dissociation of oxyhemoglobin and cerebral anoxia. Both types of cerebral anoxia occur in response to stress-producing life situations in association with feelings of desperation and defeat, exhaustion, anxiety, fear, and during the early part of convalescence. Fatigue, prostration and asthenia as experienced by patients is a complex state dependent upon emotional attitude, the absence of a dominant motivation and the presence of a stress-producing life situation with accompanying inefficiency of cardiovascular and respiratory function.

Exercise tolerance was appraised in a 48 year old housewife with complaints of chest pain for four years and hypertension, 230/130 to 140/90. She could complete only half of the standard procedure because of "dizziness." Her blood pressure, initially 140/90, increased to 160/130 with increase in heart rate. The cardiac index was lower following exercise and there was a delay in the return of the output to the resting level. Somewhat later her illness and problems connected with the behavior of her daughter were discussed. A second exercise test taken after this disturbing interview was even less well performed than the first, with more palpitations, dizziness and anxiety.

The following protocols indicate that the hypodynamic response is sometimes more clearly defined after sympathectomy.

A 43 year old male lithographer who frequently dipped his hands in chromic acid, developed arterial hypertension with left hemiparesis and Raynaud's syndrome with scleroderma. He was incapacitated and his claims for disability compensation on the basis of chromic acid poisoning were rejected by the compensation board. Discussion of this topic and the relevance of his illness to the security of his family is illustrative: During the resting or initial period the patient was slightly depressed. He was tearful and anxious during the early part of the interview and there was a rise in blood pressure, stroke volume and cardiac output. As the interview continued the patient became further depressed, with a fall in stroke volume and cardiac output, during, however, sustained elevation of blood pressure.

With the ending of the interview, although still slightly depressed, the patient became more relaxed and his stroke volume and cardiac output were reversed to the control level.

After a total sympathectomy, discussion of the same topics evoked a similar emotional response in this man. During the control period he was relatively relaxed but with the beginning of the interview he began to weep. There was now a fall in blood pressure and increase in heart rate. No significant change in stroke volume or cardiac output occurred. The patient was then diverted, the blood pressure rose, and the heart rate fell. The disturbing topics were again reviewed and again the blood pressure fell, the heart rate increased, and this time the stroke volume also fell slightly. At the end of the interview the patient became more relaxed and his stroke volume increased, returning to the initial level.

A 43 year old housewife had had hypertension with headaches and angina pectoris for some years. When studied before total sympathectomy, during the discussion of her symptoms and illness the patient exhibited mixed anxiety and depression. Her blood pressure, stroke volume and cardiac output rose with little change in heart rate. Four months later, after a total sympathectomy, the patient discussed quarrels between her husband and son. The son was unemployed, and contemplating marriage while he lived with his parents. The patient's husband looked upon this as impertinence. There were frequent quarrels and as frequently the patient went to bed for relief from her angina. She was convinced that the poor home atmosphere had caused her health to deteriorate. While discussing her situation and expressing her resentments she became extremely depressed and wept. There was little change in her heart rate, but a 25 per cent drop in stroke volume. For this woman who had suffered cardiac failure some months before, such a hypodynamic response could be ominous.

Thus, there is evidence of essentially two kinds of cardiovascular reaction during stress: (1) hyperdynamic responses or the reaction of mobilization for defense, and (2) hypodynamic responses or a reaction of defeat, quite the opposite to the preparation for fight.

These matters become important when attempts are made to evaluate the effectiveness of drugs supposedly exerting an influence on angina of effort. Gold[8] has called attention to the fact that various compounds, notably xanthines, allegedly useful, are of doubtful value in the treatment of such pain. Even when the use of such agents is recommended on the basis of improvement in exercise tolerance tests after their administration, it may not be assumed that they will improve function under other more pertinent conditions. Results of exercise tolerance tests done without knowledge of the subject's feeling states or under circumstances that leave out of account the usual work-a-day life and problems with their medley of feelings and attitudes are not easily interpreted with accuracy and permit only limited inferences.

Cardiac Arrhythmias in Periods of Stress

Extrasystoles

Electrocardiographic evidences of ventricular extrasystoles were demonstrated by Drs. Stevenson, Duncan, and S. Wolf[4] in older persons by discussing significant personal topics. These phenomena are more easily demonstrated in individuals with slightly damaged myocardia. In a series of carefully studied older persons the number of extrasystoles per hundred beats was found to parallel the intensity of outward manifestations of anxiety.

The following protocol is a representative example of the relation of life stress and the occurrence of extrasystoles. A 55 year old woman came to the hospital with the complaint of palpitations and "nervousness." She had hoped for and planned a career in music, but at the age of 17, after the onset of bilateral chorioretinitis, she abandoned it. She was by no means totally incapacitated by her inadequate vision and was able to get around easily and even to read large type. However, she did little for herself and subsided into a state of dependency upon her family, who, in turn, omitted her from the family councils and in general treated her like a child. After the death of her parents, a younger sister assumed this responsibility for her and also supremacy

among the siblings, handled all financial transactions and freely directed the patient's life. In her thirties the patient became pregnant without marriage. Retrospectively at least, she felt that the man involved would have married her but for the meddlesome interference of her family which drove him away. Her family urged her to give up her illegitimate child for adoption, but she elected to raise him herself. This she did, not unsuccessfully, with the help of her family and some financial aid from the child's father. Relations with her sister continued to deteriorate and a few years before her first hospital visit palpitations began, precipitated by altercations with the sister. She finally withdrew from the latter's home and "went on relief."

Examination revealed an obese woman with moderate hypertension (as high as 176/94). She had an enlarged heart and a systolic murmur at the base. An x-ray plate showed tortuosity and sclerosis of the aorta. Tachycardia was frequent, the heart rate during early interviews averaging about 100. There were numerous ventricular extrasystoles. The electrocardiogram showed left axis deviation. The patient was an anxious, passive, dependent person, with hostile feelings largely repressed.

During a control period preceding an interview the patient showed alternate relaxation and apprehension, the latter appearing when she focussed her attention on the electrocardiogram being recorded. During periods of such anxiety, ventricular extrasystoles were frequent, but she had none when she was able to achieve relaxation. Immediately when the interviewing physician entered the room and began to talk to her she became apprehensive as to what this might portend and at the same time began to have extrasystoles. But the physician by his words and manner reassured her and she relaxed once more, again with cessation of the extrasystoles. When, however, her illegitimate child was discussed the patient immediately became agitated and flushed, and fidgeted on the bed. Extrasystoles again appeared and continued throughout the period of agitation. After a further period of comparatively neutral conversation, frequency of the extrasystoles again diminished. The question of her future welfare was then raised and she was asked if she was sure her son would support her and not later turn against her. This distressed her almost as much as the previous question and extrasystoles greatly increased in number. Finally the patient was praised for the scholastic achievements of her son, diverted by pleasant conversation, and she became more composed and at ease. Concomitantly, the extrasystoles ceased. Throughout the interview, which extended over forty-five minutes, the heart rate was comparatively unchanged.

During the following six months, interviews with therapeutic orientation were conducted. Subsequently the patient continued to improve symptomatically, and three months after the last experimental interview reported almost complete absence of palpitations. No extrasystoles were detected in electrocardiographic records after the third interview. Also the pulse rate in successive visits was slower, dropping to 84 during the last two visits. Her blood pressure fell gradually to 132/70. Furthermore, the patient's performance of a standard exercise tolerance test (as judged by return of the pulse rate to the resting value) was improved.

In a group of 12 unselected patients with extrasystoles (similarly studied), the life situations and emotional states of the patients were found to be relevant to the occurrence of the arrhythmias. Extrasystoles were observed to occur in these subjects during discussions of topics known to arouse anxiety and which had previously been associated with extrasystoles.

The excitability of the heart may be significantly altered by prolonged hyperactivity of the cardiac muscle during anxiety with tachycardia and increased stroke volume. Structurally diseased hearts are less able to stand the strain of such hyperactivity and more readily develop altered excitability than do normal hearts. Extrasystoles are therefore particularly common in patients with structural heart disease who exhibit prolonged anxiety and the associated reactions of cardiac mobilization.

The management of subjects with extrasystoles must include attention to the life situation and the patient's adjustment to it, not only for its effect on the arrhythmia per se, which is of itself of little moment, but especially

to reduce the stress on the individual and his heart, of which the extrasystoles are an indication.

Auricular Fibrillation

Paroxysms of auricular fibrillation with life stress may be separated by many years and then occur only under circumstances of sustained and mounting tension. Thus, a 49 year old man in a high executive office during the war year 1941 and in a setting of steady and unmitigated pressure concerned with national and international affairs developed auricular fibrillation. The attack lasted about four days. The patient had a regular rhythm until almost nine years later when at the age of 58 under somewhat similar circumstances of sustained tension with insomnia, having to do with the long illness and ultimate death of his wife, he again developed auricular fibrillation. This was ended in less than forty-eight hours by the use of quinidine. Thereafter he again maintained regular rhythm.

Similar arrhythmias were exhibited by the following two patients carefully studied by Stevenson and Duncan[4] at the New York Hospital. Their protocols are presented in detail.

Patient A. A 40 year old man had been coming to New York Hospital for several years with palpitations which were due to attacks of paroxysmal auricular tachycardia and auricular fibrillation. He was born of immigrant Russian Jewish parents and brought up in poverty. The mother was the dominant member of the family. Her attitude was tyrannical and at one time she even had the patient arrested for a minor misdemeanor. He tried a number of jobs haphazardly but throughout most of his life he had supported himself by disposing of illicit goods. At the age of 34 he was markedly obese and was found to have a blood pressure of 150/105 or higher. At about this time he had his first episode of palpitations.

At 36 years of age he married a gentile girl who was was ten years younger then he. His wife proved to be, like his mother, a domineering personality and they had frequent quarrels. After being ejected by his mother they lived with his wife's family. He was obliged to accept from them both financial support and humiliation. He felt considerable resentment and much of this was transferred to his wife, who, he felt, had not adequately protected him from the assaults of her relatives.

In this patient as in others, anxiety seemed to be the largest component of the personality structure. He expressed much of his hostility to his physicians, but it was almost impossible for him to do so in the presence of those toward whom it was directed. His attitude was generally passive and dependent. He had been and was continually and fruitlessly seeking support from his mother, wife and relatives. He resented their failure to supply it more abundantly, but he was afraid that any complaint would lead to their giving him even less.

As noted, the patient was markedly obese. The blood pressure was elevated, being usually approximately 160/110. Apart from the arrhythmias frequently encountered there was little remarkable about the examination of the heart. A striking feature, noted in this and many of the other subjects of this group, was moderate tachycardia even with sinus rhythm. The rate was never found lower than 78 and varied between this figure and 100. He said he rarely slept the night before he was to report to the hospital and when he was studied he usually displayed other signs of anxiety, such as dry mouth and a tense, cracked voice.

Following a painfully humiliating experience at the hands of his brother-in-law the patient had, as usual, restrained himself from speaking. He came to the laboratory the next day in a state of tension, complaining of palpitations which had begun shortly after the episode. Electrocardiographic tracings revealed auricular fibrillation. He was urged to discuss the events leading to the attack. He began to talk about the unpleasantness at home and as he did so he became more tense. He attempted at first to suppress his emotion but, being encouraged to express himself freely, he began to weep and sob, expressing mixed feelings of resentment and depression. Six seconds after the onset of weeping numerous ventricular extrasystoles appeared, twenty-four occurring in twenty-four seconds. They persisted throughout the sobbing, but disappeared completely when he had relaxed. The basic rhythm of auricular fibrillation continued throughout and the ventricular rate of 164 remained unaltered during the period of observation.

Patient B. A 34 year old housewife was referred for study because of paroxysmal auricular fibrillation.

The patient's parents lived first in Rumania where her father was a butcher. He was quick tempered and the patient felt more attached to her mother, though she did not feel close to either parent. The first ten years of the patient's life were spent in Rumania where she lived from 1909 to 1919 when she came to the United States. She recalled the unsettled conditions in Rumania during this time, the famines and the invasion of the Germans with their foraging and raiding for food. She remembered having many illnesses during this period.

The patient described herself as "always nervous, even as a child." Her husband said "she has always been sensitive as long as I have known her and

that's since she was always bashful and also very willful and hard to manage." In youth she had had a goiter which became prominent when she was about 19 years of age. When 24 she married. Her anxiety continued throughout and gradually was blended into the full picture of hyperthyroidism. This was characterized first by amenorrhea, vomiting, diarrhea, and an increase in general nervousness. Later she showed bulging eyes and had paroxysmal attacks of palpitations and became short of breath. She persistently refused to see a doctor until the diarrhea had made her desperately ill.

Finally the diagnosis was made, a basal metabolic rate of plus 42 found, and her thyroid gland was surgically treated. Afterwards the patient "felt like a new person" for about a year. Then her brother entered the Army and her sister-in-law was obliged to work. Care of their three children devolved on the patient, who found this too much to cope with and she became "nervous" again with frequent attacks of palpitations.

After about a year in this state she was examined thoroughly and her metabolism found elevated to plus 15 with regrowth of the thyroid gland. After an unsuccessful trial of thiouracil, a second thyroidectomy was performed. Following this operation she continued to be tense and anxious and to suffer from episodes of paroxysmal auricular fibrillation, many of which were observed in the clinic. They occurred about twice a month in settings of tension and fatigue.

Examination revealed no enlargement of the heart and there were no murmurs. The blood pressure was 120/80. The heart rate was usually accelerated, almost invariably above 80 and more often around 100. X-ray examination of the chest revealed no unusual cardiac configuration. The electrocardiogram, besides showing the tachycardia, revealed the P-R interval prolonged to 0.21 seconds and a negative T wave in Lead CF_4.

The patient displayed both anxiety and compulsiveness. She was extremely meticulous about the care of her house and threw herself into housework with great energy and fretfulness, frequently exhausting herself in the process. She was a victim of insomnia and lay awake at night mulling over the day's events. She showed a quick temper after her father's fashion. "People annoy me. I don't know why. Even if I go to the theater and someone chews gum, I could scream. If things don't go my way right away, I scream." She had difficulty with decisions. She was reserved and tense during interviews and when asked to relax became more tense. Even when given 0.4 Gm. of sodium amytal intravenously she remained completely alert and said later she had been afraid "to let go," in case she might say things she did not want to say.

Her chief anxiety was her health, about which she invariably imagined the worst. Her grandmother had died of cancer and the patient attributed to cancer her symptoms of endometriosis and uterine fibroids. She became more firmly convinced of this when, after study of a vaginal smear, she was advised to have a hysterectomy although no one had suggested cancer to her. She read avidly and with alarm, articles on health and disease in popular magazines.

The patient was interviewed while electrocardiograms were being taken. Initially she was extremely tense and anxious and there was sinus tachycardia with a ventricular rate of 113. The P-R interval was 0.20 seconds. The patient's health was then discussed with her. As she described her worries over her health she became even more anxious than before. She spoke of the fear that her menorrhagia was due to cancer. As she said this she became more agitated and began to weep. The heart rate rose to 140, and then fell again to 128. She continued to be anxious and a tracing taken 30 seconds later showed the presence of auricular fibrillation with a ventricular rate of 158. This arrhythmia persisted throughout the rest of the interview, during which the patient was strongly reassured and urged to relax. She did not become aware of palpitations herself until after she had left the clinic. The attack stopped the following morning after the patient had given herself quinidine.

Following the above observations the patient was interviewed a few times in the out-patient department. She entered a period of relative calm in her life and for three and a half months had no attack whatever. Her heart rate was noted to be slower. She said, "Maybe I am more contented and at ease."

During this period the hysterectomy, previously deferred because of her arrhythmias, was performed and her husband had a minor operation. About the same time they were forced to move out of their apartment. These circumstances brought back the patient's anxiety and attacks of auricular fibrillation recurred. As before, fatigue and stressful situations were the commonest precipitating factors. Thus, one episode of arrhythmia came on after a visit to the gynecology clinic in which some misunderstood remarks of the physician filled her with anxiety. Another occurred after a visit to our clinic when she was asked if her husband would come to the clinic to discuss her illness with the physicians. She interpreted this to indicate a forthcoming revelation of bad news and again felt anxiety and developed auricular fibrillation that evening. The arrhythmias were preceded by an awareness of tension and of acceleration of the heart.

Comment. In a group of 25 unselected patients with paroxysmal auricular and nodal tachycardia and auricular filbrillation similarly studied, the life situations and emotional states of the patients were found to be most signifi-

cantly related to the occurrence of attacks. These were precipitated during periods of tension associated with anxiety, resentment, conflict and depression. When the immediate emotional reaction was intense, the attack usually occurred at the time of the associated event. When it was less severe the attack occurred some time later after an intervening period of mounting tension. The patients possessed certain personality traits which rendered them particularly subject to the development of anxiety, resentment and depression in response to only moderately stressful life situations. Precipitating events such as tripping, postural changes and being suddenly startled were also common, but were operative especially during stressful life situations and disturbed emotional states.

Electrocardiographic Changes during Periods of Stress

Precordial pain and electrocardiographic changes in persons experiencing difficulty in their interpersonal relationships were studied. A characteristic example was a patient with beginning myocardial insufficiency, who was in a state of sustained suppressed anger focussed especially upon his "in-laws." A discussion of the latter was associated with a striking increase in blood pressure and cardiac output and, as well, electrocardiographic changes during pain in the chest. These alterations disappeared when the patient felt more secure and was enabled to relax. The increase in cardiac work associated with anger made more demands than his coronary circulation and damaged myocardium could fulfill.

Drs. Stevenson and Duncan intensively studied a series of patients as regards electrocardiographic changes during spontaneously occurring and induced emotional disturbances. Thus, a 32 year old Polish housewife came to the hospital with complaints of palpitations and dyspnea, aching in the limbs and precordial pain.

Her early life had been passed in Poland where she was allegedly maltreated by her grandparents while her mother was in the United States. Later she joined her mother but felt rejected by her and displaced by a younger sister who had been born in this country. She felt lonely and after little acquaintance with men, married at 20 years of age. Her married life was unhappy and she derived little companionship from her husband and no sexual satisfaction. After the birth of a son she focussed her affections upon him and her husband drifted off into relationships with other women.

However, she continued to be emotionally dependent upon her husband, and her symptoms first came on while he was "overseas" when she felt particularly lonely. They disappeared upon his return but when his night working hours again separated them much of the time and symptoms recurred, she came to the hospital. After a series of interviews in which the emotional development of the patient and the relations of her symptoms to emotional states were discussed, she improved and was free of symptoms for eight months. At the end of that time she discovered evidence of infidelity in the part of her husband. With mingled resentment towards him and anxiety about her future, she resolved to divorce him and began to plan grimly for this step. In this setting her symptoms returned and she was interviewed in the laboratory.

At the beginning of the interview the patient was somewhat tense. When asked to think about relations with her favored sister she thought instead of her mother's inadequacy and of her own unhappy and fear-ridden childhood. Anxiety was prominent, with some resentment. The rate was 99 and the T wave in Lead III was inverted. After some discussion the patient was aksed to describe her feelings on discovering her husband's infidelity. The heart rate rose from 78 to 88 and then as she expressed deep resentment and described herself as "mad" it reached 96. At the same time the T wave in Lead III again became inverted, having a slightly different appearance from that during the earlier period when anxiety was more prominent. Associated with the changes in Lead III there was during the period of anxiety a diminution of the T wave in Lead II. Deep inspiration and expiration did not alter Lead III, but a standard exercise test effected an inversion of the T wave Lead III similar to that

which occurred during the periods of emotional disturbance.

Electrocardiograms were recorded on a total of 35 patients while they were discussing problems of great personal significance, arousing anxiety and resentment. The majority of the patients showed significant changes in heart rate and in the configuration of the electrocardiogram. In 18 patients the electrocardiographic changes would have been interpreted as abnormal had they occurred during or after standard exercise tests. These were similar to those previously described by Gold, Kwit, and Modell[9] as occurring in certain individuals experiencing severe pain during periods of noxious stimulation.

Prolonged and moderately severe tachycardia (with associated T wave changes) was observed in many patients during periods of tension and anxiety, even though they were ostensibly in a basal state. In contrast, standard exercise tests performed during periods of relative tranquility produced little rise in heart rate, followed by rapid recovery, without changes in the electrocardiographic configuration.

Patients above 45 years of age usually showed less emotional change during discussions of their own disturbing problems than did younger persons, and proportionately less electrocardiographic change. Also, under these circumstances patients with arteriosclerotic heart disease showed less tachycardia than did the group of persons without arteriosclerotic heart disease. However, when vigorous reactions were induced the configuration was clearly abnormal. A small group of patients with asthma and without complaints or evidence of cardiovascular disease showed effort intolerance and changes in heart rate and T waves as great as those observed in patients complaining of palpitations.

As a corollary of this observation, and probably of major significance, are the demonstrations of Schneider who is studying at the New York Hospital the problem of thrombosis in relation to life stress. Dramatic reductions in clotting time occur during painful experiences, vigorous effort and periods of alarm or anxiety. The pertinence of such increased clotting potential in persons with narrowed myocardial and cerebral vessels, or in those in whom blood flow is slow, especially in the presence of atheromatous placques, is self evident.

The Relation of Arterial Blood Pressure to Life Situations and Emotions

Just as there are "stomach reactors"[11, 12] and "nose reactors,"[13] there are "pulse reactors" and "blood pressure reactors."[1, 2] This specificity was dramatically demonstrated in two young physicians working under ostensibly similar conditions of stress; one reacted with no change in blood pressure but with increased pulse rate, and the other with increased blood pressure and little change in pulse rate. Also, as indicated in previous sections, abundant evidence has been assembled to show that one cannot judge the effect of life stress on the cardiovascular function purely by determination of a so-called resting level. It does not become apparent, until after adding an increment of stress such as exercise, that the individual is already reacting as though he were carrying an increased load.

So also, the response in blood pressure to the cold pressor test was shown by my colleagues, Dr. S. Wolf, John Pfeiffer and H. Ripley[14] to be dependent in good part upon the general life situation in which an individual finds himself. Thus, a patient in the last weeks of an unwanted pregnancy had, during a discussion of her forthcoming parturition, a brisk rise in blood pressure. After this traumatic interview during which she had expressed her conflicts and resentments, she felt dejected, exhausted and overwhelmed. At this time immersing her hand in ice water induced a depressor response with marked fall in blood pressure and cardiac output, resulting in her collapse with nausea and other systemic symptoms. Following delivery, when the baby had been disposed of through legal channels, the patient was much calmer and at this time had an average response to the test with slight increase in blood pressure, cardiac output and pulse rate. Obviously her pregnancy, her conflicts and her resentments had much to do with shaping the unusual nature of her first response.

Examples of variability in the degree and type of cold pressor response were frequently

encountered and studied by my associates Drs. Stewart Wolf, John Pfeiffer and Herbert Ripley.[14] Again, the significance of the event appeared to influence its effect upon arterial pressure. For example, when a 28 year old steam fitter inferred that the decision as to whether or not he would undergo a mutilating sympathectomy hinged upon the outcome of a cold pressor test, he displayed the response of a "hyperreactor" (blood pressure rise from 150/105 to 180/122 with the peak attained after withdrawal of the hand from ice water and with slow return to control level). Later on the same day, when he was assured that the operation was not considered necessary, his blood pressure was lower initially and the test produced a "hyporeactive" response (blood pressure rise from 135/85 to 150/100 and immediate return to control level). Even at times when his initial pressure was high, however, his response was "hyporeactive" when the performance of the test had no special significance for him (blood pressure rise from 160/110 to 170/110 with immediate return to control level before hand was withdrawn from ice water).

Comment. Thus, clearly there is no standard assault; it is always the assault plus its implications or meaning to the individual which determines his reaction. It is, of course, widely known that blood pressure in persons with essential hypertension does change from week to week and month to month and consideration of the individual's life situations and attitudes can be rewarding in understanding these variations.

The action of sodium amytal in reducing blood pressure is shown to be a function of the mental tranquility usually so attained and not to any particular action of the drug on the cardiovascular system, since disturbing discussion will, even during the peak of the action of sodium amytal, return the blood pressure to its previously high level or even higher.

Concerning the pathogenesis of this mobilization response, the older concepts of sympathicotonia and organ inferiority are inadequate because among hypertensives the blood pressure does not inevitably or necessarily rise in response to stress. When in reaction to a threat the subject feels defeated or overwhelmed, a depressor reaction may occur. Not only the amount but also the direction of change appears to depend on what the particular stimulus means to the subject.

Hypertension, Renal Blood Flow and Life Stress

Thirty-five subjects with and without essential hypertension were studied by my associate John Pfeiffer[15] with regard to blood pressure response and change in renal hemodynamics during interviews equivalent in their effects to the stresses imposed by the day to day experiences of the subjects. Rises in blood pressure were accompanied by evidence of intense renal vasoconstriction, associated with a fall in renal blood flow amounting to as much as 25 per cent. This persisted in some instances for as long as an hour after the blood pressure returned to the initial level. The increase in peripheral resistance in the kidney was demonstrated under these circumstances to be as much as 40 to 50 per cent.

The rises in blood pressure appear to be due in part to increase in cardiac output and in part to general vasoconstriction which follows an initial brief peripheral vasodilatation. The general vasoconstriction in the hypertensive was of longer duration than the increase in cardiac output.

The pattern of reaction did not differ among the normotensives as compared to the hypertensives except for a far greater intensity and duration of reaction in the latter. It was demonstrated that during the decrease in the effective renal blood flow, as measured by the para-amino-hippuric acid method, the stroke volume was increased. Hence it appears that under these circumstances of stress there is (1) an increase in the cardiac output, (2) there is a slight initial peripheral vasodilatation followed by a general vasoconstriction and (3) that there is an actual renal vasoconstriction. It was possible to demonstrate that this renal ischemia is probably not the primary factor in the pressor response during emotional stress, for after sympathectomy a pressor response to discussion of

a traumatic subject occurs despite an actual increase in effective renal blood flow.

In an individual with unilateral kidney sympathectomy, during relaxation the renal blood flow was equal on both sides. The renal hemodynamics of the two kidneys before, during and after an interview were compared but no inferences could be drawn since the patient failed to respond to the symbols introduced. However, it was shown in a series of patients after bilateral sympathectomy that the vasoconstriction of efferent vessels during stress is eliminated; but vasoconstriction of the afferent vessels persists, suggesting that there is either an intrinsic renal mechanism controlling the afferent vessels or there is a humoral factor operating in addition to the neurogenic.

Support for the point of view that such a pressor pattern of reaction involves the cerebral cortex as well as lower neural structures derives from the work of Pool[16] and his associates who performed bilateral topectomy on 2 psychotic subjects with essential hypertension, removing the medial portion of Brodman areas 9 and 10. Prior to operation the blood pressure of the first subject ranged between 200 and 220 systolic and 120 and 130 diastolic. For two years after operation the average range was 170 to 180 systolic and 100 diastolic. The continued moderate hypertension in this subject suggests that part of the hypertensive mechanism at least may become irreversible by the interruption of cortical pathways. The second subject has been followed for only five months postoperatively but, coincident with clinical improvement characterized by lessening of depression and decreased preoccupation with problems and conflicts, the blood pressure fell from an average range of 180 to 200 systolic and 110 to 120 diastolic to 120/80.

Also, E. Spiegel[17] produced lesions in the dorsomedial nuclei of the thalamus of a patient with schizophrenia. One year later, when this patient was last examined, a "marked drop" in blood pressure still persisted.

The data just presented indicate the profound effect of day to day situational stresses upon the cardiovascular system. The fact that rise in blood pressure and depression in blood flow through kidneys occur in both those with normal blood pressure and those with essential hypertension certainly indicates that this type of response is part of a common reaction of the total organism to threats from his environment. However, the response of both blood pressure and renal blood flow is considerably accentuated in the hypertensive group. This is also true of cardiac output and vascular reactivity of the skin. Whether this response bears any relationship to the mechanism whereby the blood pressure is maintained at an elevated level in the hypertensive individual is not as yet clear. However, the kidneys seem to operate in these circumstances under relatively anoxic conditions, and in spite of the rise in cardiac output, they do not get their proportional share of blood from the heart. This must be diverted elsewhere, possibly through the muscles. It might be considered that in reaction to stress in which the organism mobilizes its forces of defense, the visceral organs of lesser immediate importance are sacrificed temporarily in favor of the organs of offense and defense, notably the muscles and possibly the nervous system. This pattern of homeostasis, while of potential value in emergency situations, may possibly result in damage and perhaps destruction of the organism itself when it can be elicited by inappropriate stimuli and sustained over long periods of time. Thus, whatever the mechanism, these stress factors in the condition we call essential hypertension are capable of producing changes in the direction of renal ischemia which are in themselves capable of altering renal function. Admitting that the exact role of renal ischemia in essential hypertension is not defined, it is yet apparent that a method or mechanism is available for the transformation of essential hypertension into a hypertension with renal damage which might then lead secondarily to a malignant hypertension.

Not only did the renal vascular apparatus of hypertensive patients respond to threats in a more vigorously characteristic fashion, but so did the individuals as a whole. From a study of a series of patients, certain inferences about their personalities seemed justified. They were tense, wary, noncommittal, unable to obtain

satisfaction from or throw themselves wholeheartedly into any endeavor, and certainly strikingly similar features were present in the background and early development of each. My associates Drs. S. Wolf, John Pfeiffer and H. Ripley[14] found that these individuals were often outwardly serene, poised, calm, cold, obviously in charge of the situation, often very gentle and "sweet." Poised, they seemed to be "sitting on the lid." They were nonreflective and displayed a taste for dealing with problems by action. Many of them exhibited signs and symptoms of excessive skeletal muscle tension. From the standpoint of attitudes as well as circulatory physiology they were mobilized for combat, but did not engage in it against the pertinent adversary. Under a façade which seemed to indicate that they were affable and easy going, they were, nevertheless, poised to strike, but withheld their punch with a guilty fear of its consequences. At the same time they displayed a strong need to conform and keep peace. This, coupled with inability to throw themselves wholeheartedly into things because of fear and suspicion, made it difficult for them to believe strongly in anything or to derive real satisfaction from their accomplishments. They felt a need to show prowess without exhibiting aggression and continually feared that they would not succeed in doing so. One also gets the impression that the individual is alert, suspicious, cautious, not willing to make a full commitment, hard-working, hard-playing, and afraid of a show of strong feeling. This control seems to be associated with an inability to let go, or to give full expression to feelings. Thus the individual with hypertension is living in a state of perpetual preparation for action, that appropriately should last ten to thirty minutes, but which for him becomes a way of life.

Summary and Formulation

As part of the reaction to stressful life situations, notably those associated with tension, frustration, conflict, anxiety and depression the cardiovascular apparatus exhibits both hyper- and hypodynamic responses. These include alterations in the rate, rhythm, force and magnitude of cardiac contraction, change in the configuration of the heart's action potential, and modification in the peripheral circulatory resistance. During the hyperdynamic circulatory reaction, heart rate, peripheral vasomotor function and stroke volume may augment together, or one or more may increase independently of the others. In like manner, hypodynamic responses may independently involve heart rate, stroke volume and peripheral vasomotor function.

Moreover, ventilatory function is dramatically modified and ventilatory efficiency impaired. Changes in the visceral parenchymal circulation, notably in the kidney, may affect other vital functions, further jeopardizing the health and survival of the organism. Many of these alterations give rise to sensations and complaints and may cause the heart to work uneconomically. This becomes of special importance if the valves or myocardium are already damaged, leading on the one hand to a faulty appraisal of the heart's potential effectiveness, and on the other to an extra burden upon an already heavily laden organ.

Studies were made of heart rate, blood pressure and cardiac output before and after a standard exercise test in subjects with and without structural heart disease, of healthy well adjusted and relatively relaxed subjects, and those who gave evidence of various degrees of emotional disturbance. The average cardiac outputs of healthy subjects who were slightly disturbed emotionally were greater before and after exercise than those of subjects who were apparently relaxed. The difference was largely attributable to increases in stroke volume. In studies over eighteen months the resting cardiac output and response to exercise fluctuated closely in relation to emotional state in patients with anxiety, and, as well, in normal subjects. Subjects with frank, overt anxiety averaged greater cardiac outputs before and after exercise than less anxious though poorly relaxed subjects. The overtly anxious patients exhibited usually a high heart rate with a normal or slightly elevated stroke volume. Healthy relaxed persons accomplished the same work with a slower rate and larger stroke volume. In general there was a close correlation between

symptoms such as dyspnea, palpitations and weakness on exertion and impaired exercise tolerance. In 10 subjects with structural heart disease similarly studied, the same relationship was found between emotional disturbances and the occurrence of symptoms and signs of effort intolerance. The symptoms themselves were similar to those associated with cardiac failure. Changes in the emotional state were accompanied by changes in exercise tolerance. In seven instances, dramatic alterations in exercise tolerance were observed during a period of less than an hour. During sustained periods of stress the resting cardiac indices were commonly normal values, while the indices after exercise became abnormal. As improvement in the feeling state progressed, complete return of exercise tolerance to normal was repeatedly noted.

During periods of emotional tension with anxiety, conflict, frustration or depression, the circulatory phenomenology in patients with hypertension and structural heart disease is similar to that of normotensives with intact hearts in like circumstances of conflict and tension. In patients with structural heart disease, symptoms originally attributed to the structural defects may be found to be related more to the reversible exercise intolerance and circulatory dysfunction associated with the reaction to stressful life situations than to structural defects. The condition known as neurocirculatory asthenia is seen, not as a permanent or fixed disease entity, but as a circulatory disorder which may fluctuate widely in any one individual and which may be found also in healthy persons during stress, and in patients with structural heart disease.

Thus, during periods of life stress impaired circulatory efficiency may result either from hyper- or hypodynamic reactions. Most commonly impaired exercise tolerance during emotional disturbances results from exaggerated cardiac mobilization in response to symbolic stimuli. Burdens imposed on the heart by everyday physical exertions are often mild and usually brief in duration and therefore are less costly as compared with those associated with emotional disturbances which may be severe and prolonged. The increased cardiac work and excessive tachycardia at rest and in response to exercise during anxiety may be relevant to the increased susceptibility of patients with tachycardia to the development of structural heart disease.

In a group of 25 unselected patients with paroxysmal auricular and nodal tachycardia and with auricular fibrillation, certain life situations and emotional states were found to be most significant factors in the occurrence of attacks. When the emotional reaction to an incident was intense the attack was usually precipitated at the time of the associated event; when it was less severe the attack was initiated some time later after an intervening period of mounting tension.

The patients studied possessed certain personality features which rendered them particularly subject to the development of anxiety, resentment and depression. Precipitating events such as tripping, postural changes and being suddenly startled were common, but were operative mainly during periods of sustained life stress and associated anxiety, conflict, frustration, resentment and depression. Especially striking were the instances of auricular fibrillation initiated during such periods of stress.

Electrocardiograms recorded on a group of 35 patients with precordial complaints during interviews involving topics of great personal significance demonstrated not only changes in rate and rhythm but alterations in the configuration of the action potential itself. In 18 patients the electrocardiographic changes found in an ostensibly basal state would have been interpreted as abnormal had they occurred during or after standard exercise tests. Prolonged and moderately severe tachycardia with associated T wave changes were most commonly observed. In contrast, standard exercise tests performed during periods of relaxation produced little rise in heart rate or change in electrocardiogram and were followed by rapid recovery.

It was possible to demonstrate in a series of patients with hypertension that methods of adjustment to life situations, attitudes and feeling states were extremely pertinent to the level of

blood pressure. Thirty-five subjects with and without essential hypertension were studied in regard to blood pressure responses and changes in renal hemodynamics during interview circumstances which induced many of the commonly experienced feeling states and reactions of these individuals. Those with essential hypertension had pressor responses of far greater magnitude and duration than did normotensives. The changes in renal circulation were correspondingly intense and prolonged, persisting in some instances for as long as an hour after the blood pressure had returned to the initial level. The pressor responses were due in part to increases in cardiac output and in part to general vasoconstriction, the latter appearing after an initial vasodilatation and persisting longer than the increase in cardiac output.

It is postulated that the hypertensive individual responds vigorously and in an inappropriate fashion to stress and regardless of whether this process is involved in the genesis and development of essential hypertension, the bodily changes so induced may contribute to the vascular and parenchymal renal damage associated with the disease.

It has also been demonstrated that the vascular alterations during periods of life stress in the mucous membranes of various parts of the stomach,[11] bowel,[12] air ways[13] and genitourinary apparatus[18] are profound and in certain instances linked with tissue damage and disease. Equally profound and coupled with great discomfort and embarrassment, though perhaps less disastrous and threatening to the survival of the organism, are the dramatic changes in circulation that occur in the skin.[19]

An amassing body of data demonstrates further the growing importance to medicine of the recognition that, for man, reactions to threats in the form of symbols, especially when sustained, may be more important than response to assaults. Certainly, many aspects of cardiovascular disease may be looked upon as functions of man's goals, his methods of achieving them, and the conflicts they engender.

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Clinical Studies on Veratrum Alkaloids

I. The Action of Protoveratrine and Veratridine in Hypertension

By EDWARD MEILMAN, M.D., AND OTTO KRAYER, M.D.

The action of two pure veratrum alkaloids, veratridine and protoveratrine, in human hypertension is described for the first time. The vasodepressor reflex pathway involved in the response to these ester alkaloids is reviewed. Protoveratrine is found to produce a striking fall in blood pressure in both essential and renal hypertension after intravenous administration.

THE USE of veratrum alkaloids in clinical medicine began many years ago[1] for a variety of indications because of their ability to decrease blood pressure and heart rate, to induce sweating and reduce the body temperature, and to prevent certain types of convulsions, especially those of eclampsia. MacNider[1] quotes the old clinical observation concerning the use of veratrum alkaloids in eclampsia: that if the "pulse was kept at or below sixty-five beats per minute, the patient could not have convulsions."

The clinical use of veratrum alkaloids has generally fallen into disrepute mainly for two reasons. The alkaloid content and composition of the plant extracts, called veratrum, vary greatly and reliable methods of standardization of the active principles are not available. Veratrum causes severe toxic reactions such as nausea, vomiting, and unpredictable and sometimes profound fall in blood pressure.

Despite these drawbacks certain obstetric clinics have continued to use veratrum viride as an adjunct in the treatment of eclampsia.[2] More recently, there has been a revival of the use of veratrum viride in the treatment of hypertension,[3] stimulated by experimental, pharmacologic work, which has led to a clarification of the mechanism of action of some of the veratrum alkaloids.

Nomenclature. In this and subsequent publications the terms "veratrum alkaloids," "veratrum," and "veratrine" will be used in conformity with the suggestions made by Krayer and Acheson.[4] The term "veratrum alkaloids" refers to all alkaloids found in any of the *Veratrum* species.* The term "veratrum," which for some time was an official name, refers to the galenical preparations of certain species of *Veratrum*. The two most commonly used and best known preparations of veratrum are "veratrum viride" from *Veratrum viride*, Aiton, and "veratrum album" from *Veratrum album*, Linn. The term "veratrine" refers to the mixture of alkaloids obtained from the seeds of *Veratrum sabadilla*, Retz., more commonly known as *Schoenocaulon officinale*, Gray.

Reflex Vasodepressor and Cardiodecelerator Action. The reflex pathways commonly considered to regulate arterial pressure are those arising in the pressoreceptor areas of the carotid sinus and of the aortic arch. Their importance as moderators of blood pressure is well known since the work of Hering[5] and of Heymans and Bouckaert.[6]

A similar vasodepressor reflex pathway which arises in the heart and has afferent fibers in the vagus nerve has not yet received much attention in the English and American literature. The evidence for the existence of this vasodepressor reflex is largely based on studies of the effect of veratrum alkaloids.

Von Bezold and Hirt[7] described a vaso-le-

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* It was pointed out by Krayer and Acheson[4] that the application of the name "hellebore" to the *Veratrum* species is incorrect and should be discontinued in the scientific literature.

pressor and cardiodecelerator action of veratrine in 1867 in laboratory experiments and attributed it to a reflex originating in the heart. This was generally forgotten until Jarisch and Richter[8] restudied it in 1939. Like von Bezold and Hirt they concluded from their experiments that the reflex decrease in heart rate and in blood pressure caused by small doses of veratrine originated predominantly in the ventricular myocardium and that the afferent impulses were carried by nerve fibers running in the vagus nerves. Jarisch and Richter proposed the name "Bezold effect" for this phenomenon.

Further evidence for the existence of such a reflex pathway came from the work of Amann and Schaefer[9] who demonstrated afferent fibers in the cardiac branches of the vagus which carried bursts of electrical activity in phase with the heart beat. These discontinuous discharges could be changed to a continuous discharge by the action of veratrine. Jarisch and Zottermann[10] have recently corroborated this observation and have further elucidated the nature of the nerve fibers.

Krayer and his collaborators[11, 12, 13] have confirmed and extended the pharmacologic work, using not only veratrine and veratrum viride but also pure veratrum alkaloids. It was shown in experimental animals that not all veratrum alkaloids but only some of the ester alkaloids like protoveratrine (from *Veratrum album*, Linn) or veratridine (one of the constituent alkaloids of veratrine) were capable of eliciting the reflex decrease in blood pressure and in heart rate, and that it was essential to use small doses to obtain the effect in its purest form. While the afferent impulses caused by veratridine[11] and protoveratrine[12] originated predominantly in the heart and lungs, a participation of the carotid sinus area also was suggested by some of the experiments. This was recently established by Aviado and Pontius.[14] By localized injections of protoveratrine and veratridine into sections of the coronary vessels, Davies[13] was able to show that the most important receptor area for this reflex was in the region of distribution of the left coronary artery of the dog and cat and, more precisely, in the area of the left circumflex branch, that is, in the left ventricle.

The efferent pathways of the reflex arc are known only in part. The cardiodecelerator impulses are carried by fibers running in the vagus and cardiodeceleration can be abolished by atropine.

The increased blood flow in various vascular areas which accompanies the blood pressure fall is due to nervous influences and not to a direct action of the alkaloids upon the vasomotor effector in the vessel wall. The mechanism by which the vasodilatation is brought about is unknown; to what extent decrease in vasomotor discharge, or vasodilatation by some other mechanisms, is involved has not been elucidated.

The receptors for this reflex pathway have not yet been anatomically demonstrated, and no reliable information is at hand as to its physiologic and pathologic role. The existence of a receptor mechanism in the left ventricle, the stimulation of which leads to a fall in blood pressure, suggests the possibility of its participation in such clinical phenomena as the profound fall in blood pressure attending severe episodes of coronary artery disease with and without infarction, or the rare return to normal or near normal pressure in the hypertension of a patient who has had a myocardial infarction.

Necessity for the Use of Pure Substances. The pharmacologic studies with pure veratrum alkaloids have revealed that several distinct properties of the alkaloid mixtures, veratrine, veratrum viride, or veratrum album, are vested in different alkaloids or alkaloid groups; hence many of the pharmacologic and clinical observations with such alkaloid mixtures were obviously due to the composite action of various substances.

We have undertaken the clinical study of the ester alkaloids, protoveratrine and veratridine, because we believe that "only the study of the pure veratrum alkaloids will permit a correct evaluation of the practical usefulness of the pure alkaloids as well as of their mixtures, and thus make possible the development of a rational basis for their clinical use."[14] Furthermore, the disagreeable side effects of veratrum

viride or veratrum album probably are vested in certain alkaloids to a higher degree than in others. This is suggested, for example, by the difference in the respiratory action of protoveratrine and veratridine in laboratory animals. The search for compounds with desirable therapeutic action and devoid of side effects can only be successful if pure substances are investigated individually.

The following is a report of studies in human hypertension in which protoveratrine has been used for the first time. A number of observations were made with veratridine, which was employed earlier in a few clinical trials.*

Substances and Methods

As has been shown by Craig and Jacobs,[16] Prelog and Szpilfogel,[17] and Rochelmeyer,[18] the veratrum alkaloids are modified sterols and their alkamines have a chemical relation to the genins of the cardiac glycosides.

Protoveratrine is a crystalline substance, $C_{39}H_{61}O_{12}N$. It is an ester alkaloid of the alkamine protoverine and the three acids, acetic acid, methylethylacetic acid, and methylethylglycolic acid. It is one of the main alkaloids of *Veratrum album* and has not yet been isolated from *Veratrum viride*. It is the most poisonous of the veratrum alkaloids so far studied and on intravenous injection in mice has an LD_{50} of 0.06 micromols (= 0.048 mg.) per kilogram.[12]

Veratridine is an amorphous alkaloid, $C_{36}H_{51}O_{11}N$. It is an ester of the alkamine cevine and one molecule of veratric acid. It is one of the alkaloids of veratrine and has not been found in either *Veratrum viride* or *Veratrum album*. Its toxicity is less than that of protoveratrine. On intravenous injection in mice it has an LD_{50} of 0.63 micromols (=0.42 mg.) per kilogram.[12]

The sample of protoveratrine used in this study was prepared from *Veratrum album*, Linn., by W. A. Jacobs of the Rockefeller Institute for Medical Research. The sample of veratridine was isolated from veratrine, Merck, by R. P. Linstead and D. Todd of the Department of Chemistry, Harvard University. The same samples of protoveratrine[12] and veratridine[15] were used in their pharmacologic studies by Krayer and his collaborators. For clinical use the alkaloids were brought into solution with N/10 hydrochloric acid and adjusted to a concentration of 1:1000 (veratridine) or 1:10,000 (protoveratrine) with distilled water. The solutions were kept at pH 6 and were sterilized by filtration through fritted glass. Maintained at 6° C. they were stable for three months.

Protoveratrine was administered by intravenous injection. One hundred sixty-eight experiments were made in 26 patients, most of them outpatients who came in for the experiments. The highest single intravenous dose given at one time was 0.20 milligram.

Veratridine was administered to 14 patients, seventeen times intravenously and seven times intramuscularly.

All blood pressure measurements were made by the same observer (E.M.) with the mercury sphygmomanometer keeping the patient in a recumbent position. Continuous observation of the electrocardiogram was made possible by the use of a cardioscope.

Results

Protoveratrine

Vasodepressor Action. Protoveratrine when administered intravenously in suitable dosage produces a fall in both systolic and diastolic pressure which is reproducible on repeated use of the same dose. Figure 1 illustrates the response of systolic blood pressure, diastolic blood pressure, and heart rate in a 50 year old woman with essential hypertension for at least five years, possibly fifteen years, who received 0.107 mg. intravenously on each of five occasions, two of them on the same day. The fall in blood pressure produced is essentially the same each time, and it is usually maximal in the first ten to fifteen minutes. Similar results were obtained in other patients with renal hypertension as well as essential hypertension. A 42 year old woman who had chronic glomerulonephritis for twelve years, during the last six of which she gradually developed hypertension, received the same dose (0.107 mg.) on each of four successive days and the response was essentially the same each time.

The amount of protoveratrine which causes a given fall in blood pressure varies from patient to patient, but in each patient, above a minimal dose, an increase in dose causes an increased effect in the dosage range studied. Larger doses cause greater fall in both systolic and diastolic blood pressure. Figure 2 shows the relation between the dose of protoveratrine in micrograms per kilogram and maximum fall in mean pressure (one-half the sum of the sys-

* These were made by Dr. E. L. Pratt at the Children's Hospital, Boston, Mass., 1944.

tolic and diastolic pressure) in 6 hypertensive patients.

In general, doses of 1 microgram per kilogram, or less, have little or no effect. Above this level and up to 3 micrograms per kilogram there is an increased response with increasing doses. Larger doses have not yet been tested.

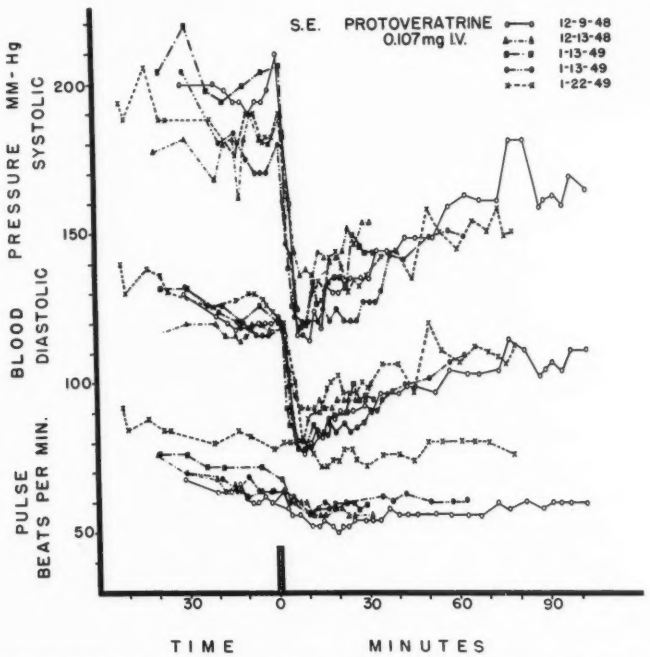

FIG. 1.—The response to the same dose of protoveratrine on five separate occasions in S.E., a 50 year old woman with essential hypertension. Weight 64.5 kilograms.

The duration of action is variable, depending on the dose as well as on the patient. In some patients the duration seems to be prolonged with larger doses. Figure 3 illustrates different durations of action in 2 patients with essential hypertension. The first patient, a man, N. P., had a vasodepressor action lasting about one and one-half hours from 0.16 mg. intravenously. In the second, a woman, S. E., a smaller dose intravenously caused a vasodepressor response that had not completely worn off in two and one-half hours. One patient with hypertensive encephalopathy and chronic pyelonephritis had a profound fall in pressure, but the duration was only about twenty minutes. In other patients, duration of three hours was not unusual.

Cardiodecelerator Action. The fall in blood pressure is accompanied by a decrease in heart rate. This is a sinus bradycardia of vagal origin and can be abolished by atropine. Figure 4 illustrates the response to a dose of protoveratrine in a patient with essential hypertension and compares it to the response when the same dose is given simultaneously with sufficient atropine to produce an acceleration in pulse rate. Although the fall is somewhat less than with protoveratrine alone, a striking fall in both systolic and diastolic blood pressure occurs despite the concomitant increase in heart rate. Thus bradycardia is not essential for the vasodepressor effect. In some patients the simultaneous administration of atropine produces a more gradual fall of blood pressure. In 2 patients, administration of atropine during the hypotensive phase produced a transient

return to the original hypertensive level during the period of tachycardia.

Cold Pressor Test. The response to the cold pressor test is not abolished during the hypotensive period following administration of protoveratrine. However, in 8 of 10 patients examined the rise in pressure produced by immersing the hand in cold water during the hypotensive period was much below the usual resting blood pressure of the patient. For example, a patient whose blood pressure rose from 176/116 to 214/138 with the cold pressor test had a rise of only 126/80 to 146/84 after the intravenous administration of protoveratrine;

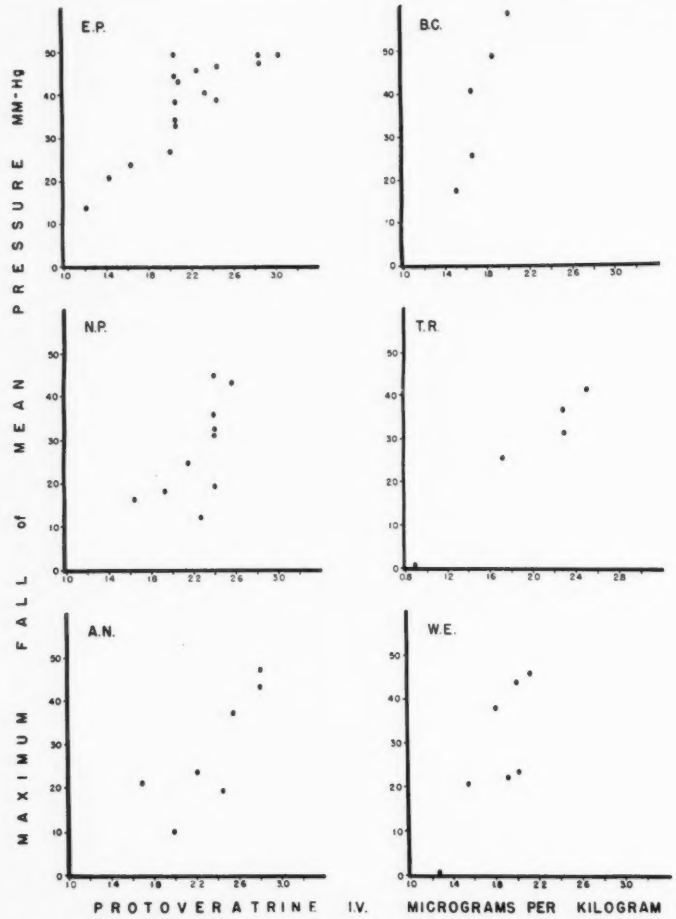

FIG. 2.—The relation between the intravenous dose of protoveratrine in micrograms per kilogram and the maximum fall in mean pressure (one-half the sum of diastolic and systolic pressure). Patient E.P. was a 42 year old woman, weighing 52.3 Kg., with chronic nephritis and hypertension. Patient B.C. was a 50 year old woman, weighing 64.5 Kg., with essential hypertension and hypertensive heart disease. Patient N.P. was a 46 year old man, weighing 66 Kg., with essential hypertension. Patient T.R. was a 39 year old man, weighing 67.3 Kg., with essential hypertension. Patient A.N. was a 52 year old woman, weighing 69 Kg., with essential hypertension. Patient W.E. was a 51 year old man, weighing 83.8 Kg., with essential hypertension, hypertensive renal, cardiac, and cerebral disease, bilateral lumbodorsal sympathectomy.

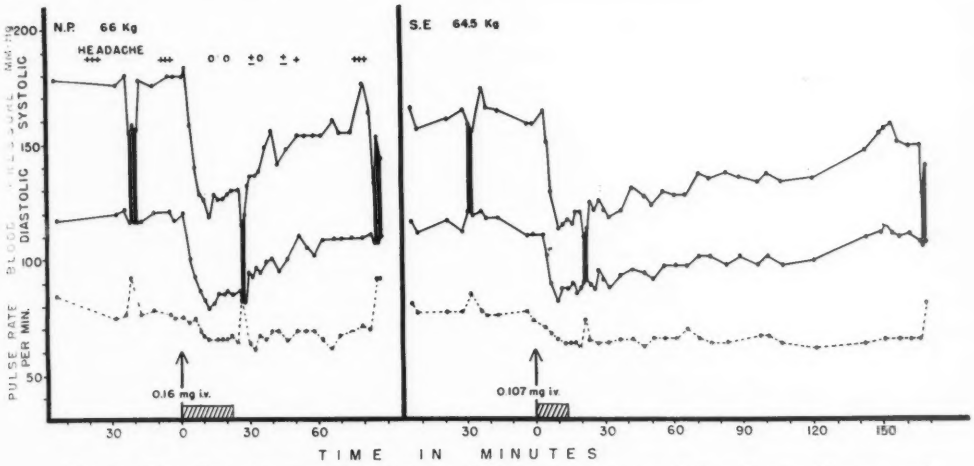

FIG. 3.—The effect of erect posture before and after protoveratrine. N.P. a 46 year old man, and S.E., a 50 year old woman, both had essential hypertension. The solid black areas represent the blood pressure with the patients in the erect position; all other lines represent values found with the patients recumbent. The hatched areas represent the duration of the subjective warmth after intravenous injection of protoveratrine. In the graph of N.P. is also illustrated the response of hypertensive headache to the hypotension induced by protoveratrine (+++, severe headache; 0, no headache; ±, intermittent headache).

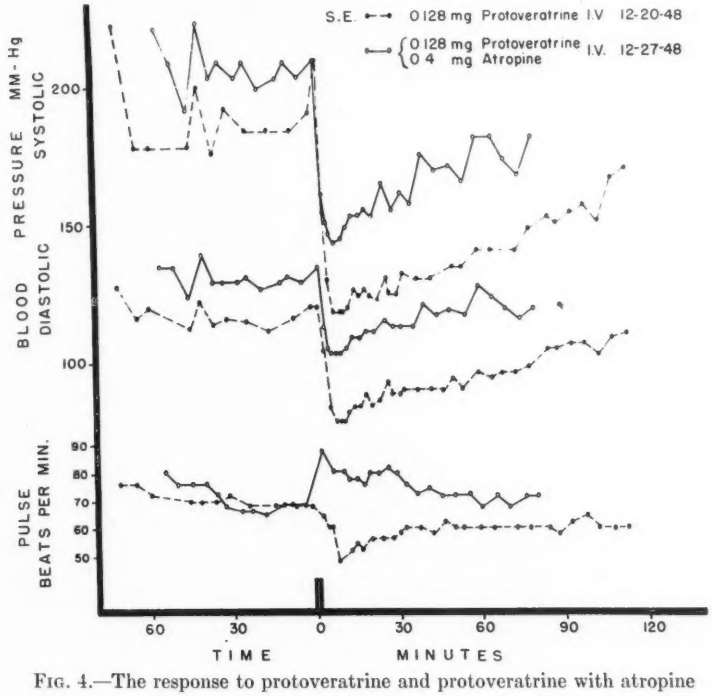

FIG. 4.—The response to protoveratrine and protoveratrine with atropine

another had a cold pressor response of 166/114 to 210/142 before and 116/78 to 130/100 after protoveratrine.

Effect of Erect Posture on Blood Pressure and Heart Rate. In more than half of forty experiments a moderate postural hypotension occurred, affecting the systolic level more than the diastolic. It did not differ much from the postural response before the drug was administered. In some patients, assumption of the erect position led to a more profound diastolic as well as systolic fall in pressure, particularly at the time of maximum action of the protoveratrine. Postural hypotension was always associated with an increase in heart rate (fig. 3).

Subjective Sensations. In every instance the intravenous administration of a large enough dose of protoveratrine produced a subjective sensation of marked warmth in the face, mouth, throat, hands, epigastrium, perineum, and feet, which was not unpleasant. The intensity of this warm feeling, its extent, and its duration of action (ten to twenty-five minutes) were proportional to the dose (fig. 3). It appeared sooner than the first change in blood pressure, was most marked during the period of rapid fall, and waned thereafter until it was completely gone before any marked rise in blood pressure towards previous hypertensive levels could be observed. The areas of most intense warmth seem to be those areas most richly supplied with sensory nerves. This sensation of warmth was not accompanied by flushing. In six instances sweating on the forehead was noted.

With the highest doses given, which varied in different patients from 0.12 to 0.20 mg., there was frequently slight dizziness during the period of warmth. This was aggravated by quick motions of the head or eyes but was only apparent when the subject's eyes were open and was transient, lasting only as long as the warm sensation. It appeared in 9 patients, eleven times as a slight light-headed feeling and nine times as definite dizziness. It is probable that large enough doses will produce this symptom in any patient. In 5 patients on eighteen occasions large doses caused a pressing, choking sensation in the epigastrium and substernally with a tendency towards deep, sighing respirations. The question naturally arises whether this symptom is due to myocardial ischemia. Of the 2 patients in the series with angina pectoris neither experienced this substernal oppressive feeling after intravenous protoveratrine despite falls in blood pressure from 210/120 to 108/74 and 184/120 to 106/76. This sensation of pressure usually lasted about ten minutes, occasionally fifteen minutes, and was most marked during the period of rapid fall in pressure. Nausea was noted thirteen times by 6 patients. It was of slight intensity nine times and of significant degree four times. Vomiting was not observed.

Although the administration of protoveratrine is attended by these subjective sensations, it may abolish other sensations presumably due to the hypertension. Five patients were given protoveratrine while suffering from headache. In one there was no response; in 2 there was mild relief attending the fall in blood pressure; in 2 (as in fig. 3) a severe headache was completely alleviated during the hypotensive period. It recurred intermittently as the level of the blood pressure rose somewhat and returned in its original intensity when the blood pressure approached initial levels.

T-Wave Changes. Many reports give the return of an inverted T_1 to upright as evidence of a salutary effect of a particular antihypertensive program (sympathectomy,[19] "rice diet",[20] Vertavis[3]). Electrocardiograms made before treatment are compared with those made several months after treatment. In our experiments four of eight patients who had the pattern of left axis deviation with flat or inverted T_1 had reversion of T_1 to upright during the period of lowered pressure and a return of the upright T wave to a flat or inverted wave as the effect of the drug wore off and the blood pressure rose towards previous levels. This was observed twenty-eight times, usually in the dosage range of 0.10 to 0.12 milligram. Figure 5 illustrates a typical response. Administration of protoveratrine produced these changes only when a good hypotensive response was obtained.

Cardiac Arrhythmias. Doses of protoveratrine of the order of 3 micrograms per kilogram (or 2 micrograms per kilogram in patients whose resting pulse rate is 60, or less) may produce

transient cardiac arrhythmias. The first change is marked sinus bradycardia which may be followed by first-degree heart block or complete block with nodal rhythm. In the 168 trials, first-degree heart block occurred four times, nodal rhythm twelve times, ventricular extrasystoles twice, bigeminy twice, and Wenckebach phenomenon twice in 10 patients, of whom 4 were digitalized. When these arrhythmias appear, they are usually intermittent. Runs of regular rhythm alternate with runs of prolonged P-R interval or nodal beats.

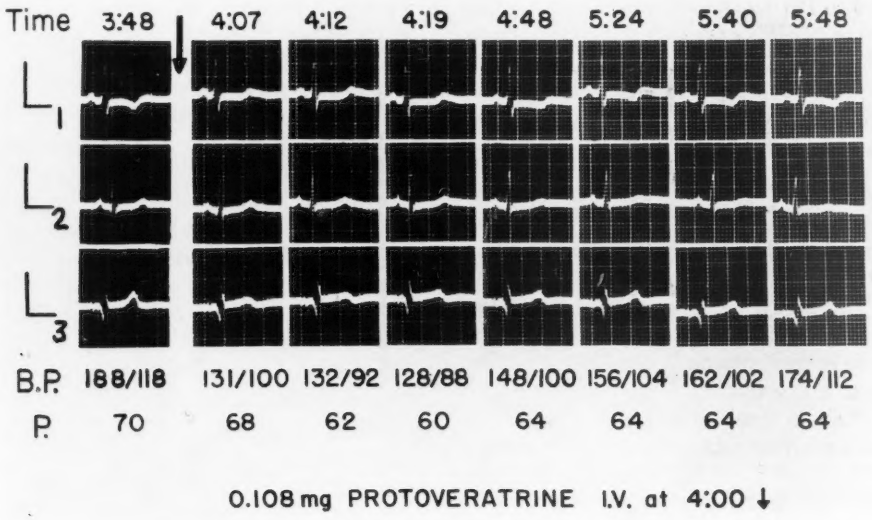

FIG. 5.—Changes in the T-wave after protoveratrine. The patient, J. F., a woman 49 years of age, had essential hypertension.

The arrhythmias appear about ten to fifteen minutes after injection and usually last a few minutes. If the dose which produces arrhythmia is given simultaneously with atropine, no arrhythmia appears; yet, a blood pressure fall still occurs, although of lesser degree. That atropine can abolish the arrhythmia once it is established was illustrated by an experiment in which a slow heart rate, induced by 0.16 mg. of protoveratrine intravenously, was associated first with prolonged P-R interval and then with 2 to 1 heart block. A subcutaneous injection of 0.8 mg. of atropine sulfate caused the appearance of Wenckebach phenomenon, then regular rhythm with P-R = 0.28 second and, a few minutes later, regular rhythm with normal P-R interval.

Patients who are fully digitalized may show electrocardiographic changes, such as increased P-R interval or bigeminy at lower doses of protoveratrine. In one fully digitalized patient, administration of 0.1 mg. intravenously produced a P-R interval of 0.4 second which lasted over two hours, whereas other patients have received almost twice that amount without arrhythmia. A patient with auricular fibrillation, who was well digitalized so that his heart rate was 52, had bigeminy for six minutes after a 0.11 mg. intravenous injection and for nine minutes after a 0.12 mg. intravenous injection.

Veratridine

As in the anesthetized dog,[15] the vasodepressor and cardiodecelerator action could be obtained by small intravenous doses. However, the response lasted only several minutes and was of only moderate degree. It was almost always attended or preceded by disagreeable side effects. Doses of 0.1 mg. produced only the peculiar subjective warmth and taste simi-

lar to that experienced after protoveratrine injection. Intravenous doses of 0.2 mg. provoked transient irregular respirations or even severe spasmodic coughing associated with a tight, choking feeling in the throat. In some instances a pressor response was observed.

Larger doses, up to 2.2 mg., were given intramuscularly, usually in divided doses. There were no disturbances of respiration. Only slight or no fall in blood pressure or heart rate occurred at doses that produced nausea, vomiting, and sweating except in one patient in whom there was a marked fall in pressure from 240/110 to 120/80 and a decrease in heart rate from 80 to 52. This was accompanied by nausea, vomiting, sweating, and apprehension. Atropine abolished the bradycardia but did not affect either the hypotensive response or the nausea and vomiting.

Discussion

These studies have borne out the supposition that individual veratrum alkaloids may be found which in a dosage range causing satisfactory clinical circulatory effects have insignificant side effects or none at all. Protoveratrine is such an alkaloid and it is possible that other ester alkaloids may be found which are as suitable or even better for clinical use than protoveratrine.* It is obvious that the ester alkaloid veratridine does not belong to this group and scarcely warrants further clinical trial.

The difference in toxicity between the two substances raises an important pharmacotherapeutic problem. The absolute toxicity, even if it is very high, does not in itself exclude a substance from those with potential clinical usefulness, provided the therapeutic efficacy is correspondingly high. Thus, protoveratrine with its high toxicity has also a high therapeutic efficacy, while veratridine which in the toxicity tests referred to was only one-tenth as toxic as protoveratrine, nevertheless, is clinically useless because its therapeutic efficacy is within the dosage range leading to severe side effects.

The upper range of the dosage of protoveratrine for therapeutic application is not yet definitely established. It should be remembered that protoveratrine is an exceedingly potent drug, and it is prone to lead to severe toxic effects if the therapeutic range is carelessly transgressed. Increasing the dose beyond a certain low range, in order to obtain greater effect, is as likely in the human as in the laboratory animal not to give better results. It is the relatively low effective dosage range employed in this study which is most apt to show reflex hypotensive action exclusively.[4]

The chemical relation to the cardiac glycosides has its parallel in the pharmacologic action upon the mammalian heart. It consists not only in an improvement of contractility of the failing heart by appropriate doses of protoveratrine but in toxic effects by larger doses on impulse conduction and generation of impulses similar to those caused by the cardiac glycosides. The observations presented above suggest that the action of the cardiac glycosides and the action of the veratrum alkaloids on the heart may be additive; hence special care is needed in gauging the dose in a patient who is under the influence of cardiac glycosides.

Conclusions

Protoveratrine and veratridine, two pure veratrum alkaloids, have been administered to human beings with hypertension. Protoveratrine can produce a significant fall in blood pressure lasting one to three hours at doses free of serious side effects. It causes a decrease in heart rate occurring simultaneously with the blood pressure fall. This can be annulled by atropine without, as a rule, abolishing the vasodepressor effect. The effects of posture and cold pressor test have been described. An inverted or flat T wave in Lead I in the electrocardiogram may revert to upright during the hypotensive period. Veratridine has an effect of similar nature but of shorter duration. It is less potent than protoveratrine and clinically useless because the dosage range leading to serious side effects is identical with, or even lower than, the range of therapeutic dosage.

* The practical usefulness of protoveratrine in maintaining generally reduced blood pressure by intramuscular injections at appropriate intervals is being studied and will be the subject of a future report.

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The Intermediary Metabolism of Cholesterol

By KONRAD BLOCH, PH.D.

Animal tissues synthesize cholesterol from metabolities of small molecular size, principally cholesterol. This synthetic process is known to take place in the liver but may also occur in other organs. In all tissues, with the exception of brain and nerve, cholesterol is continually regenerated. Cholesterol is the parent substance which the animal organism uses to produce bile acids, progesterone and possibly also other steroid hormones. The catabolism of cholesterol leads to the formation of several saturated, metabolically inert sterols, cholestenone presumably being the common intermediate.

IT IS widely believed that arterial disease, specifically atherosclerosis, is associated with derangements in the metabolism of cholesterol. This view is largely based on two findings: the fact that atherosclerotic aortae contain abnormally large amounts of cholesterol, and the demonstration that by feeding of cholesterol a condition resembling human atherosclerosis can be induced experimentally in rabbits. To correlate these phenomena with specific events in the metabolism of cholesterol has so far not been possible. Wide gaps exist in our present knowledge of the intermediary metabolism of cholesterol even under normal conditions and it is likely that the elucidation of the role of cholesterol in arterial disease must await the solution of some of the basic problems in cholesterol metabolism.

In the following report no attempt will be made to review the literature which deals with the relationship of cholesterol metabolism to atherosclerosis. Instead, some aspects of the metabolism of cholesterol in normal animals will be discussed in the hope that this may stimulate investigations which are more specifically concerned with the behavior of this compound in various pathologic states.

Cholesterol is derived from the hydrocarbon cyclopentanoperhydrophenanthrene, a structure which occurs widely and in numerous modifications in living cells. Although sterols are found in plants and in certain micro-organisms, cholesterol itself is specifically a constituent of animal cells. In view of the ubiquitous distribution of sterols it has been speculated that these compounds are essential components of the cell, an attractive hypothesis but for the fact that none of the known steroids are essential for the functioning of the bacterial cell. Therefore, the role of steroids in cellular metabolism appears to be more specialized than this hypothesis would indicate. In animal tissues cholesterol is found in all body cells and as far as is known the content of cholesterol is remarkably constant in various nutritional states excepting those which involve excessive feeding of cholesterol itself.

Cholesterol is not required as an essential dietary constituent since synthetic, sterol-free diets are adequate for growth and maintenance of most animals. In this respect the larvae of certain insects[1] and some parasites[2] form a notable exception. For these organisms, sterols are indispensable dietary components. It can be stated, however, that the large majority of animals is capable of synthesizing the steroid structure from generally available food elements. Until recently, sterols of plant origin were considered to be supplementary or even exclusive sources of cellular cholesterol. The studies dealing with sterol absorption, which have been carried out by Schoenheimer[3] and Page,[4] have made it appear likely that sterols of other than animal origin are not significantly absorbed from the gastrointestinal tract and consequently that they cannot serve as adequate sources of tissue cholesterol. It is interesting to note that in the rabbit, which is highly susceptible to the experimental atherosclerosis by cholesterol feeding, even excessive amounts of plant sterols such as sitosterol show

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no harmful effect[5] and this indicates that in omnivorous and herbivorous animals alike the conversion of plant to animal sterols is not significant. The findings relating to the lack of absorption of plant sterols call attention to the unique selectivity which characterizes the intestinal absorption process with regard to sterols. Slight alterations in the structure of the molecule interfere with the passage through the intestinal wall. Those few cholesterol derivatives which are adsorbed are also known to play a role in the intermediary metabolism of cholesterol, notably cholestenone and 7-dehydrocholesterol. Further studies are needed to ascertain whether intestinal absorption is restricted to those sterols and sterol derivatives which are products of the intermediary metabolism.

Since it has been recognized that animals obtain steroids from endogenous syntheses, the nature of the processes leading to the formation of cholesterol and other steroids has become a challenging problem. The ability of animal cells to carry out the total synthesis of the steroid structure has been demonstrated in recent years by both direct and indirect experiments. Balance experiments with animals on diets of known composition have shown that the deposition of cholesterol in the tissues during growth is greatly in excess of the uptake of sterols from the diet.[6, 7] Therefore, the extra cholesterol in these experiments must have been of endogenous origin. These balance experiments, which have been carried out with various animal species, have been important in establishing the occurrence of the over-all process of steroid synthesis but have failed to disclose details of the mechanism. On the other hand, somewhat more concrete information on various aspects of the biosynthesis of cholesterol has been obtained with the aid of the tracer technic which has more recently been applied to this problem. The utility of the tracer technic in the study of steroid synthesis as well as for biochemical syntheses in general derives from the fact that it permits the detection of processes which occur in the so-called steady state. Steady-state reactions cannot be followed by ordinary analytic procedures because they do not result in a net change of the concentration of reaction products and reactants respectively, synthesis and degradation of the metabolite taking place concurrently. Since steroid synthesis has so far been observed only in systems containing intact cells, i.e., under steady-state conditions, it is clear that the tracer technic is uniquely suited to the study of this process. The first instructive experiment with tracers was performed in 1937 by Rittenberg and Schoenheimer[8] who administered heavy water to mice and studied the rate at which isotopic hydrogen was incorporated into the tissues' lipids. The incorporation of deuterium into cholesterol from a heavy-water medium is the result of chemical reactions and the speed at which it occurs provides a measure of the rate at which the cholesterol molecules present at the beginning of the experiment are replaced by newly synthesized cholesterol. This rate is moderately rapid for the cholesterol of most tissues and one can calculate that, for instance, the cholesterol in the liver of the rat is regenerated or rejuvenated at a rate corresponding to a half-life of less than ten days.[9] The results obtained by Rittenberg and Schoenheimer suggested that cholesterol is formed by a process of total synthesis which involves the condensation of numerous small-sized molecules rather than by modification of a preformed steroid structure such as those of plant steroids. We have extended these findings and have tested the isotopically labeled forms of a number of small molecular compounds with respect to their ability to yield labeled cholesterol in rats and have found acetic acid to be the most efficient precursor.[10, 11] There are other compounds which like acetic acid give rise to isotopic cholesterol but they are probably not precursors or intermediates in the sense that they are specifically utilized. They merely serve as sources of acetic acid which in turn provides the basic building blocks. Cholesterol which is biologically synthesized from labeled acetic acid has been degraded chemically by various procedures[12, 13] to ascertain whether the entire sterol structure or only a limited portion of the molecule is derived from these small units. So far, acetic acid carbon has been encountered in all fractions which have been investigated,

and the available evidence suggests that the majority if not all carbon atoms of the steroid structure are contributed by acetic acid. No theory can be offered at present to explain the synthetic mechanism by which these small units are joined to yield the complex steroid structure. Intermediates which by their chemical nature might provide clues to the reaction mechanism have not been isolated to date. Moreover, since complex compounds such as steroids require for their synthesis intact cellular systems a study of cholesterol synthesis in simple systems of known compositions is not feasible at the present time.

Synthesis of cholesterol can be demonstrated under in vitro conditions as well as in the intact animal.[14] The reaction takes place readily in slices of surviving liver but comes to a complete standstill when the organization of the liver tissue is destroyed by grinding or homogenizing of the cells. By using test substances labeled by C^{14}, which permits detection of synthetic activities of a very small order, it can be shown that in a liver preparation which contains no intact cells cholesterol synthesis proceeds at a rate less than one ten-thousandth of the rate which is observed in slices. It appears, therefore, that the synthesis of cholesterol requires the cooperation of various enzymes which are suitably organized in space. This condition is fulfilled only in the intact cell. We have not been successful in demonstrating the occurrence of cholesterol synthesis in testes, spleen, intestine, kidney and heart, but it would be unwarranted to state at this time that cholesterol synthesis is confined to the liver. The brain is the only organ which may be excluded as a site of cholesterol synthesis. Waelsch, Sperry, and Stoyanoff[15] have maintained growing rats on a heavy-water regimen and have shown that the appearance of newly synthesized cholesterol in the brain is arrested when myelinization is complete. The metabolic inertia of brain cholesterol can also be demonstrated by feeding of labeled acetate to rats. The isotope concentrations in cholesterol formed from acetate vary from organ to organ and follow roughly the order of metabolic activities which have been observed for other tissue constituents such as fatty acids and proteins. It appears that the newly formed cholesterol is rapidly distributed from the site of synthesis throughout the body. The brain and central nervous system, however, do not participate in this distribution process, nor does the brain appear to be capable of synthesizing cholesterol.[16] The singular behavior of brain cholesterol is also illustrated by an experiment in which a dog was injected intravenously with labeled cholesterol. The labeled material was subsequently encountered in every organ with the exception of brain and spinal cord.[17] Thus, the relatively large masses of cholesterol in the central nervous system are metabolically inert and here the function of cholesterol does not seem to be associated with any chemical reactions but evidently must reside in some physical or structural properties of the molecule.

The factors responsible for regulating the rate of cholesterol synthesis have not been explored, but there is reason to believe that in normal animals this rate is little affected by variations in dietary composition. A rather striking gradation of rates is observed when cholesterol synthesis is investigated in slices of surviving rat liver. In this system the isotope concentration in cholesterol depends very critically on the age or weight of the animal from which the liver is taken. The isotopic values in cholesterol for the two extreme age or weight groups were found to differ[14] by a factor of more than 10. An extension of these experiments in the direction of both younger and older animals will be necessary before the significance of these observations can be evaluated.

All attempts to accelerate cholesterol synthesis in vitro beyond the rate which is observed by simply placing liver slices in a buffer medium in an atmosphere of oxygen have so far been unsuccessful. Apparently, the liver tissue contains endogenous substrate in amounts which are adequate to allow cholesterol synthesis to proceed at optimal rates for several hours. This is in contrast to the synthesis of other lipid material such as fatty acids which are also synthesized from acetic acid units as the principle precursor.[18] In a saline-buffer medium, fatty acid synthesis proceeds

slowly but can be stimulated by the additions of substrates, such as glucose and pyruvate, which serve as energy sources.[19] The addition of pyruvate markedly stimulates fatty acid synthesis from acetate, but affects cholesterol synthesis adversely. It is evident from our data that under certain conditions the isotope concentration in cholesterol can greatly exceed that in the fatty acids showing that the higher fatty acids are not intermediates in the conversion of acetate to cholesterol. Another example may serve to illustrate the differences in the mechanism responsible for fatty acid and cholesterol synthesis respectively. In the absence of calcium ion, fatty acid synthesis in surviving liver is strongly inhibited while cholesterol synthesis is much less affected.

It should be emphasized that in the in vitro experiments which have been cited the rate of cholesterol synthesis is calculated from the extent of isotope incorporation without consideration of any change in total quantity of cholesterol which might occur. The rate of synthesis which is observed, although actually of the same order as it occurs in the intact animal, corresponds to a few per cent only of the cholesterol originally present in the tissue. A change of this magnitude could not be detected by the methods available for quantitative cholesterol analysis. Indeed, it is quite conceivable that the synthesis which we observe is not associated with a net change but that the quantity of sterol remains constant during the experimental period. In this case we would deal with a dynamic equilibrium, synthesis being balanced by simultaneous destruction of cholesterol in vitro as well as in vivo.

While the first portion of this discussion has been concerned with the total synthesis of the steroid molecule, I would like to consider now a number of anabolic and catabolic reactions which represent modifications of the cholesterol structure and which yield the excretion products and the various steroids of specialized function. Under conditions of nutritional equilibrium the quantity of cholesterol in animal tissues is constant and products of cholesterol catabolism must be formed at the same rate at which cholesterol is newly synthesized. The daily excretion of fecal sterols corresponds roughly to the quantity of cholesterol synthesized during the same time interval. Hence, in animals which are kept on a sterol-free diet, the sterols excreted in the feces, which consist mainly of coprosterol, account for the bulk of the catabolic products. A different situation may arise when the exogenous supply of cholesterol is increased. As shown by Page and Menschick[20] and later by Schoenheimer and Breusch,[7] in balance experiments, destruction of cholesterol takes place in the tissues when the quantity of cholesterol in the diet becomes abnormally high. It appears that the mechanisms which are responsible for the conversion of cholesterol to fecal sterols become saturated and that excess exogenous cholesterol enters an alternative metabolic path. The so-called cholesterol destruction which takes place under such conditions has not been defined chemically and may not, therefore, be taken too literally. It merely indicates that products are formed which are no longer precipitable by digitonin but which may still have an intact steroid nucleus.

The pathways leading to the end products of cholesterol metabolism have been investigated extensively. There is evidence from several sources that the first step is a dehydrogenation to cholestenone and that this unsaturated ketone is the common precursor of coprosterol, dihydrocholesterol, and probably also of epicoprosterol. Page and Menschick have presented evidence for the occurrence of cholestenone by showing that the sterols from atheromatous lesions contain a fraction which has the same spectral absorption maximum as cholestenone.[21] Later, Rosenheim and Webster[22] succeeded in isolating cholestenone in considerable quantities from rat and dog feces. Schoenheimer, Rittenberg and Graff[23] by using partially labeled cholestenone have demonstrated that in the dog and the human cholestenone is converted to coprosterol. In our laboratory, additional evidence for the occurrence of this unsaturated ketone in cholesterol metabolism has been obtained.[24] After the administration of deuteriocholestenone to rats, a high isotope concentration was found not only in the fecal sterols but also in the sterols

from the tissues. The deuterium concentration was particularly high in the fraction containing the saturated sterols which consist essentially of dihydrocholesterol. Cholestenone can therefore be converted into both dihydrocholesterol and coprosterol. On the other hand, the cholesterol isolated from the same experiment contained only a small excess of isotope showing that the transformation of cholesterol to cholestenone is not readily reversible. These experiments also demonstrate that cholestenone in contrast to most derivatives of cholesterol is absorbed from the gastrointestinal tract. One of the aspects of cholesterol catabolism which has not been settled satisfactorily concerns the site at which these conversions take place. Coprosterol has not been found in the tissues proper and it is therefore believed that bacterial action in the gut is responsible for its formation.[25] On the other hand, it is probable that at least the initial step in the conversion, namely, that of cholesterol to cholestenone, occurs in the tissues themselves. Whether intestinal bacteria can reduce cholestenone to coprosterol has not been tested. A second problem which deserves further attention is the effect of dietary variations on the composition of fecal sterols. The relative proportions of unsaturated and saturated sterols in the excreta are known to vary widely and, as Rosenheim and Webster[26] have shown, the degree of saturation is controlled by dietary factors. A clarification of these relationships is desirable because derangements in cholesterol metabolism which lead to an accumulation of cholesterol in the tissues may well reflect an insufficiency of the mechanisms which effect the conversion of cholesterol to excretory products.

The only specific role in metabolism which can at present be assigned to cholesterol is that of a precursor of steroids of specialized function. It has long been suspected that cholesterol and the structurally related steroids are also interrelated biochemically. Direct experimental evidence for the existence of such relationships has recently been furnished in two specific instances. Cholesterol has been identified as the principal precursor for cholic acid[17] and for progesterone.[27] In both cases the proof for these transformations is based on the demonstration that the administration of isotopically labeled cholesterol results in the formation of labeled bile acid and steroid hormone respectively. The data indicate that these conversions are direct without disruption of the basic steroid ring structure. The total synthesis of the steroid skeleton from small building blocks such as acetic acid therefore appears to lead to cholesterol as the principal product, while bile acids and steroid hormones are formed secondarily by a modification of the pre-existing steroid structure of cholesterol. An origin from cholesterol is also strongly indicated for the steroid hormones of the adrenal cortex. The work of Long and his associates has shown that adrenotropic hormone causes a marked decline of the cholesterol in the adrenal cortex suggesting that this cholesterol deficit is due to the formation of cortical steroids.[28] Similar evidence points to cholesterol as the parent substance of the estrogenic hormones. Ovarian activity and therefore an increased output of estrogens has been shown to be accompanied by a decrease of cholesterol in this organ.[29] Experimental technics which permit a direct study of the biologic interrelationships of the divers steroids are now available and it should be possible, therefore, to establish whether cholesterol is indeed the primary source of all compounds having the steroid structure.

The quantities of cholesterol which are available in various tissues of the animal and which are continuously replenished by endogenous synthesis are far in excess of the quantities required for the production of steroids of specialized function. It is therefore unlikely that the metabolic reactions of cholesterol are confined to processes which involve chemical alterations of the cholesterol molecule of the type mentioned. For example, since cholesterol occurs in tissues both in the free form and esterified with fatty acids it is likely that cholesterol plays some role in the metabolism of fatty acids. In any case there is sufficient evidence to indicate that cholesterol possesses a variety of functions in intermediary metabolism, and it is probably correct to say that its chief functions are still unknown.

The investigations which have been dis-

cussed here have served to emphasize the necessity of considering intermediary metabolism in terms of the rates of synthesis and destruction of a given tissue constituent. Clearly, the evaluation of metabolic events on the basis of concentration changes alone is inadequate. In the specific case of cholesterol it may be asked whether a condition associated with an increased sterol level in a given tissue or body fluid is the result of an accelerated synthesis or of a decline in the rate of catabolic and anabolic conversions. A change of the level of cholesterol which is observed in a pathologic condition may then acquire a different meaning and might be indicative of the site and the nature of the metabolic derangement. Only scant attention has been paid to these aspects of metabolism, largely because traditional technics did not lend themselves to this type of analysis. The tracer technic opens an approach to these problems and it may be hoped that it will be of aid in the understanding of metabolic disorders.

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Resection of an Aneurysm of the Arch of the Aorta with Preservation of the Lumen of the Vessel

By Olivier Monod, M.D., and André Meyer, M.D.

A case is reported of a 20 year old woman, without history, stigmata, or serologic evidence of syphilis, who presented a mediastinal mass just above and lateral to the arch of the aorta which was originally mistaken for tuberculous lymph nodes. The diagnosis of saccular aneurysm was made after direct puncture of this mass under pleuroscopy. Exploratory thoracotomy was performed and a saccular aneurysm of the terminal part of the arch of the aorta was found. The aneurysm was removed and the aorta sutured without interrupting the continuity of the artery or narrowing its lumen. The authors believe that this is the second successful resection of an aortic aneurysm and the first in which resection was accomplished with preservation of the lumen of the aorta.

WE WISH to present an unusual case report of a 20 year old girl from whom a saccular aneurysm of the arch of the aorta was removed without disturbing the flow of blood through the aorta. Since we have been unable to find a similar report in the literature, we are reporting the case history in detail.

Case Report

On Nov. 29, 1947 a 20 year old unmarried woman was admitted to the Boucicaut Hospital on Dr. André Meyer's service for evaluation of a rounded opacity shown by roentgenographic studies of the chest.

Early in 1945 she had had a persistent occipital headache which was accompanied by fever and which lasted three weeks. No treatment was given. In October 1945 the patient felt a "stitch" in the side at the right lung base which was accompanied by weight loss and a cough. A chest film seemed to reveal a few "spots" on the right side and a rounded opacity on the left side which was considered a tuberculous cavity. The tuberculin skin test was positive. The patient spent fifteen months in a sanatorium. Hemoptysis was never present and repeated gastric washings before and after admission to the sanitorium were negative for the Koch bacillus.

The past medical history revealed the occurrence of chicken pox, measles, and mumps in childhood. At the age of 7 years a small node which contained "some black blood" was removed from the left axilla.

From Laënnec Hospital, Department of Thoracic Surgery, Service of Dr. Olivier Monod, and Boucicaut Hospital, Service of Dr. André Meyer, Paris, France.

Roentgenographic Studies. When we saw the patient in November 1947, x-ray films of the chest revealed a more or less circular shadow localized just at the outside and to the left of the aortic arch (fig. 1). The opacity was homogeneous and the shadow had a sharply demarcated outline. The surrounding pulmonary tissue was normal. A lateral film showed the opacity to be in the central part of the mediastinum. At 7.0 cm. from the dorsal plane, tomography revealed the opacity to be in continuity with the opacity of the aorta (fig. 2). This opacity measured 4.0 by 5.0 by 5.0 centimeters. Except for this shadow, the chest was considered to be normal. The ribs were not notched and radioscopy did not show any pulsation or expansion of the abnormality after a left-sided pneumothorax was induced (fig. 3). The temporary lack of Diodrast prevented us from making serial arteriographs.

As a result of these studies the diagnosis of a tuberculous lesion was abandoned and the lesion was considered to be probably a mediastinal tumor of neurogenic origin.

Pleuroscopy. A pleuroscopic examination, which is customary in such cases, was made on December 9, 1947 and a smooth, yellowish-white, spherical tumor was observed.* No intrinsic pulsations were noted and the tumor seemed to move in unison with the pulsations of the aorta. The metallic "palpateur" revealed the tumor to be quite hard. It was independent of the lobes of the lungs and was localized

* The pleuroscopic examination was made by Dr. Nico.

opposite the forward part of the vertebral bodies on the superior and left side of the aortic arch. Under direct vision the tumor was punctured by a needle and pure bright red blood was withdrawn. Following removal of the needle a pulsatile stream of blood ran from the puncture for a few moments.

In view of these findings the diagnosis of neuroma was abandoned and the diagnosis of a vascular tumor or aneurysmal sac of a large artery, probably the aorta, was substituted.

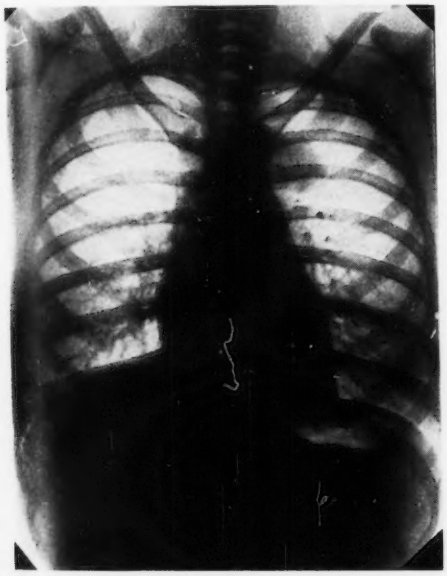

FIG. 1.—X-ray film made July 4, 1947. A rounded shadow is seen just outside and to the left of the aortic arch.

Physical Examination and Laboratory Studies. At this time the state of health was excellent in every way. There was no fever or emaciation. The heart sounds were normal. The blood pressure in the left arm on December 2, 1947 was 175/100 (Vaquez). On December 4, 1947, the blood pressure in the right arm was 150/115 with a maximum oscillometrical index of 6; in the left arm, 165/100 with an oscillometric index of 4 (Pachon). There were no signs of coarctation of the aorta such as pulsation of the intercostal, scapular, external mammary, or internal mammary arteries. The eyegrounds were normal. Cytologic and chemical examination of the urine was within normal limits, as were the tendon and cutaneous reflexes. The electrocardiogram revealed sinus rhythm, a heart rate of 120, and "predominance of the right side."

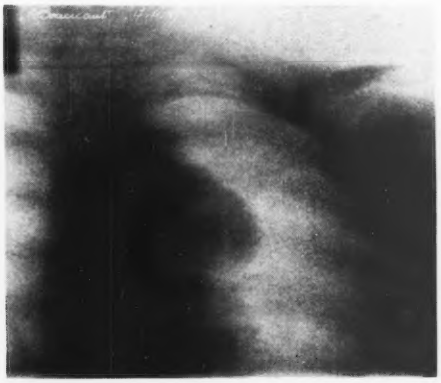

FIG. 2.—Tomographic study at 7.0 cm. from the dorsal plane. The shadow is seen to be in continuity with the aorta.

FIG. 3.—X-ray film made after left pneumothorax.

There was slight prominence of Q_2 and Q_3. The blood Wassermann reaction was negative on three occasions before and after the operation and there was no history or stigmata of syphilis. The blood urea nitrogen was 15 mg. per cent;

the red blood cell count was 3,320,000; and the white blood cell count was 4,800.

A thoracotomy was decided upon with the thought that, if a tumor or cyst was found, it would be removed. If it proved to be an aneurysm, a decision would be made at operation as to just what could be done surgically.

Operation. An operation was performed by one of us (O. M.) on December 24, 1947. The anesthetic* consisted of cyclopropane and ether, given by inhalation with tracheal intubation and a closed circuit. During the operation 300 cc. of physiologic saline, 500 cc. of plasma, and 800 cc. of whole blood were given intravenously.

A lateral thoracotomy was performed with resection of the fifth rib from the transverse process to the cartilage. The sixth rib was cut at the posterior angle and the pleura entirely freed. A subpleural tumor localized below and to the left of the terminal part of the arch of the aorta became visible. The tumor was very distended and did not pulsate. (We were aware that the absence of this last sign does not eliminate the possibility of an aortic aneurysm, as was shown by Alexander and Byron[1]). The pleura was mobile on the surface and it was easy to separate all of the surface of the tumor, as would be the case with a cyst without any pericystic reaction. The vagus nerve was seen in front of the arch of the aorta and on the right of the tumor which was connected with the left side of the aortic arch by a fairly large pedicle. During the separation of the tumor, a small tear occurred at the most bulging and thinnest part of the sac, but the hemorrhage was immediately stopped by forceps. The pedicle of the sac was then thoroughly isolated and the aorta was carefully stripped of its cellular sheath. Two Crafoord clamps were set longitudinally on the aorta so as to exclude the zone of the pedicle without entirely stopping the aortic blood stream.

The pedicle was then cut. After the pedicle was severed, it could be seen that the opening of the aneurysmal sac into the aorta was fortunately in the form of a slit. The opening was along the long axis of the aorta, being approximately 4.0 cm. long but relatively narrow. This made it possible to close the opening in the aortic wall without narrowing the lumen of this vessel. A continuous suture was carefully introduced to bring into apposition the endothelium of each lip. The stitches were placed about 0.2 mm. apart and extended into the arterial wall to a depth of 0.5 millimeters. A second continuous suture, also perforating the muscular wall of the aorta, was made for security. The temporary hemostasis was then loosened. The material used for the suture was a nonabsorbent and nonabsorbable silk.

During the operation, care was taken to respect the vagus and the left recurrent laryngeal nerves which crossed the aortic arch 2.0 mm. in front of the pedicle of the aneurysmal sac.

The region was then explored and it was noted that below the suture a large anomalous artery arose from the convexity of the terminal part of the aortic arch. This artery was directed upward and to the right, passing between the spine and the esophagus. It was from this trunk that the brachial and cephalic arteries arose.

The whole of the apex of the parietal pleura was detached, as if for extrapleural pneumothorax, to furnish a good pleural flap for the operative zone. In this way all the operative zone was covered with pleura. The wound was sutured in three planes after complete re-expansion of the lung.

In the course of the operation, no increased vascularization of the intercostal muscles was observed. The intercostal arteries, as well as the medium-sized and small vessels of the mediastinum, showed a normal caliber.

Pathologic Findings. The gross specimen was a saccular aneurysm that was nearly spherical. Externally it was fairly regular with, nevertheless, two broad bulging areas which were not particularly prominent. The surface was smooth, white, and anatomically and surgically well separated from surrounding structures. The wall was of moderate thickness but of less thickness than the aortic wall. It was very thin at the level of the two bulging areas. The internal surface of the sac was smooth and white. There was no sign of clot formation nor

* Anesthesia was under the supervision of Dr. Delahaye.

of inflammation. The appearance was the same as that of the internal surface of the aorta. However, on certain parts of the surface, one could see small flattened areas, separated columns, and falciform folds.

The histologic examination was performed by Dr. Dobkevitch and Professor Lenègere and is reported verbatim. "The histologic examination enabled us to identify the elements of an arterial wall. The adventitia was abnormal, being very much sclerosed. A certain amount of inflammatory perivascular reaction with an accumulation of spongy cells was observed. The elastic substance was badly damaged. The elastic fibers of the media were irregularly thickened and discolored; the appearance was sometimes granular. These fibers were absent in whole areas. Elastic and muscular fibers were separated by fibrous tissue. The internal elastic lamina occasionally appeared to be discontinued or cleaved. Finally, there seemed to exist a certain amount of elastification of the intima.

"Thus, the lesion actually involved an arterial wall in which characteristic elements were recognized. This wall was severely damaged and misshapen. The elastic substance was especially damaged. Histologic examination justified no precise statement concerning the origin of this process."

Postoperative course. The postoperative course was quite normal. Cardiac drugs that might raise the blood pressure were avoided. One million units of penicillin were given daily for ten days. Thoracenteses were performed on the second day (350 cc.), third day (30 cc.), fifth day (50 cc.), sixth day (225 cc.), seventh day (25 cc.), and on the eighth day (10 cc.). The extrapleural space created by the mobilization of the pleura was also drained on the nineth day and 100 cc. of fluid were removed. The stitches were removed on the ninth day. Postoperatively, auscultation of the anterior chest revealed no cardiac abnormalities. Posteriorly, a systolic murmur was heard over the spine. This was thought to be due to the anomalous artery passing between the esophagus and the spine. Blood pressure readings in the four extremities were normal. A chest film taken seven weeks after operation revealed an opacity at the level of the pleural detachment (fig. 4).

The patient was seen again on March 20, 1948. She had resumed her normal life. At that time it was decided to examine her regularly as we remained dubious about the future of the aortic suture.

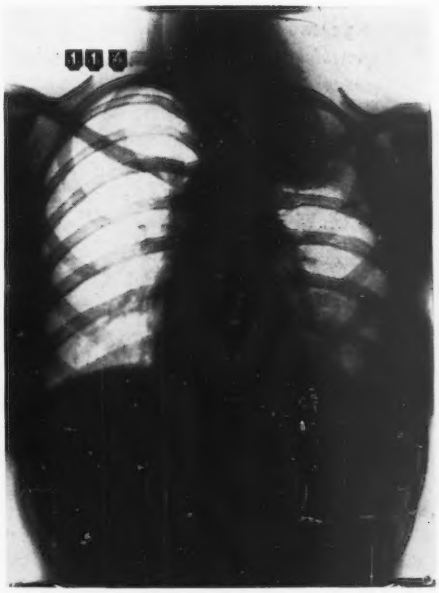

FIG. 4.—X-ray film made seven weeks after operation. The opacity is the result of detachment of the pleura which was used to reinforce the sutured aorta.

DISCUSSION

Our case is the first in which an aneurysm of the aorta was resected with preservation of the vessel's lumen and recovery of the patient. As far as we know, only one other aneurysm has been successfully resected, but in this instance interruption of the continuity of the artery was necessary.[1] In this classic case, which was reported by Alexander and Byron,[1] the aneurysm which was removed was a fusiform and not a saccular one. Their patient, a 19 year old man, whose blood Wassermann reaction was negative on three occasions, showed all the signs of occlusion of the aorta. The blood pressure was 160/70 in the arms and undetectable in the legs. Erosion of the ribs and other evidences of a developed collateral

circulation were present. At operation pulsation of the aorta was seen to be vigorous above the aneurysm and imperceptible below it. After removal of the involved portion of the aorta the blood pressure in the arms rose to 260/130 and after ten days dropped to a level around 220/130, at which level it remained until the patient's death from a cerebrovascular accident two years after operation.

Pathogenesis. Syphilis was not the etiology in our case: the history was not suggestive, the blood Wassermann reaction was repeatedly negative and there were no inflammatory lesions in the wall or in the cellular tissue. It was necessary to consider the possibility that the structure we dealt with was a congenital lesion, perhaps a diverticulum of the aorta. The coexistence of the aneurysm with an anomaly in the distribution of the branches of the aortic arch is not a very strong argument in favor of a congenital origin since such anomalies are comparatively frequent, whereas congenital aneurysms of a size comparable to the one which we removed must be exceptional, if they exist at all.

Fusiform or spherical dilations of the aorta have been known to exist below an aortic constriction but we found no sign of stenosis of the vessel.

We regard the lesion which we operated upon as a dissecting aneurysm, due, perhaps, to an embolus to a vessel of the aortic wall or to an arteritis resulting from variations of blood pressure. The areas of necrosis of the media led us to consider the last possibility.

Diagnosis. When the patient was first studied, the clinical findings suggested tuberculosis. When this disease was eliminated, a benign tumor was thought of. This consideration was based on the absence of suggestive symptoms and on the radiographic outline. Pleuroscopy, by which we were able to introduce a needle into the tumor and obtain pure blood, enabled us to correct the diagnosis. Within our personal experience, this is the third time that puncture under pleuroscopy made clear a diagnosis of aortic aneurysm.

Surgical Considerations. From the anatomic and surgical point of view, we will remember the characteristics of the sac wall. The constituents of the wall were well differentiated and showed under the microscope the differentiated layers of the aorta. The wall was thin, even very thin in some places. It was cleavable, dissectable, and without adhesions due to inflammation. It was elastic and suturable, though very fragile. The stitches had to pass through the normal aortic coats in order to hold. The vagus nerve helped us find our bearings and to protect the recurrent nerve. The mobilization of the pleura by the use of the extrapleural pneumothorax, which has been our accustomed practice, was of invaluable aid in covering and strengthening the suture line.

The indications for operation are debatable. Our intervention was proposed as an exploratory operation. Only after seeing the aneurysm did we decide upon resection. Our case was an exceptional one. We do not believe, generally speaking, that syphilitic aneurysms can be removed.

Summary

We have presented what we think is the first case in which an aneurysm of the arch of the aorta was removed successfully without disturbance of the continuity of the lumen of the aorta.

REFERENCE

[1] Alexander, J., and Byron, F.: Aortectomy for thoracic aneurysm. J.A.M.A. **126:** 1139, 1944.

Gangrene of the Extremities of Venous Origin
Review of the Literature with Case Reports

By Henry Haimovici, M.D.

Gangrene of the extremities of venous origin is reviewed; it is a rare but distinct clinicopathologic entity hitherto not widely known. A classification of the cases of thrombophlebitis complicated with gangrene is presented, based on the presence of the peripheral pulses: (1) cases with palpable arteries; (2) cases with nonpalpable but patent arteries. Patency of the entire arterial system of the involved extremity, as verified by anatomic findings, is necessary for correct diagnosis. Complete blockage of the venous system appears to be the initiating and main cause, angiospasm playing a secondary role. The gangrene usually remains superficial and limited. Hence, a conservative surgical attitude is emphasized.

GANGRENE of the extremities due to vascular disturbances can almost invariably be ascribed to either pure arterial occlusion or mixed arterial and venous occlusions. Gangrene as a result of venous obstruction alone is a third variety, but its possibility is not widely recognized. This paper will deal with this latter variety only.

The common clinical course of the occlusion of the main vein of an extremity is well known. The absence of anoxemia of the tissues in thrombophlebitis or phlebothrombosis is explained by the ease with which the collateral circulation is re-established owing to the abundant venous pathways. When, however, in addition to the main vein most, if not all, of the tributaries are also occluded, marked anoxemia of the tissues leading to gangrene may ensue from the sole obstruction of the venous tree.

Gangrene following extensive thrombophlebitis without arterial occlusion is, however, of rare occurrence. A perusal of the literature has uncovered only 27 such cases, with adequate clinical and pathologic information. Two of these were observed by the author.

Historical Data

As early as 1593, Fabricius Hildanus[1] seems to have been the first to recognize the possibility of gangrene of venous origin. Ever since, more particularly during the eighteenth and early nineteenth centuries, there has been much discussion on this subject as attested by many case reports. However, most of these reports were probably those of cases of gangrene due to mixed arteriovenous obliteration. Undoubtedly, the description of these cases suffered from the confusion which existed at that time regarding the whole subject of gangrene and its mechanism. In the latter part of the nineteenth century the clinical and pathologic descriptions of some of these cases seem to leave no doubt about their diagnosis.

Cruveilhier,[2] in his "Traité d'Anatomie Pathologique Générale" (1862), pointed out the extreme rareness of this condition and emphasized that only very extensive venous thrombosis of both the main and collateral trunks can cause it.

In 1859, Hueter[3] published the report of a case and gave an excellent account of the clinical and pathologic criteria of this type of gangrene. In 1894, Gaillard[4] reported a similar case and reviewed the previously published observations. Most of the latter, however, upon careful analysis cannot be accepted as bona fide cases of gangrene due to venous occlusion alone. Three years later, Reyt[5] observed another case and again reviewed the subject. Thereafter it is surprising to note that for more than three decades the literature carried only one new observation published in 1905 by Pons.[6]

In 1924, in his book, Buerger[7] merely mentioned that "complete obstruction of the chief veins of a part, without occlusion of the arteries, may also lead to moist gangrene, although this is of rare occurrence." In a further chapter he simply emphasized the fact that "in the veins only extensive thrombosis over large territories is effective in producing gangrene of an extremity or portions of an extremity."

Bergendal[8] revived the subject in 1931 by reporting another case of "gangrene of the foot and lower part of leg in consequence of venous thrombosis." In the following years, several clinical and pathologic reports were published by Bergeret, Guillaume, and Delarue in 1932[9]; Wertheimer and Frieh in 1935[10]; Gutzeit in 1936[11]; Fontaine, Israel, and de Souza-Pereira in 1936[12]; Salmon, Audier, Jouve, and Haimovici in 1938[13]; Gregoire in 1938[14]; Pringle in 1938.[15]

In 1937, Fontaine and de Souza-Pereira[16] reproduced experimentally this type of lesion in the dog by the division of all the veins at the root of the

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TABLE 1. SUMMARY OF CASES

Case Author Date	Sex Age	Etiologic bases	Site of thr-phl.	Clinical aspect of the venous occlusion	Peripheral pulses	Extent of gangrene	Treatment	Result	Anatomic findings of the vessels of the affected extremity	
									Veins	Arteries
1, Hueter,[3] 1859	M 43	Unknown	RLE	a. Phl. a. dol. b. 11 days later phl. caer. dol.	Ant. tib. felt. Post. tib. n.r.	Foot & lower leg	—	Died. Pulm. emb.?	Thrombosis of all veins distal to com. iliac	Patent. Dissection distal to com. iliac
2, Gaillard,[4] 1894	F 27	Gastric ca.	LLE	Phl. caer. dol.	Only fem. felt	Foot	—	Died	Thrombosis of all veins distal to fem.	Patent. Dissection distal to fem.
3, Reyt,[5] 1897	M 18	Pulmonary T.B.	RLE	a. Phl. a. dol. b. 21 days later phl. caer. dol.	Only fem. felt	Foot	—	Died	Thrombosis of all veins distal to vena cava	Patent. Dissection from heart to toes
4, Pons,[6] 1905	M 35	Post-traum. (fracture of femur)	RLE	Phl. caer. dol.	Only fem. felt	Foot & lower $\frac{2}{3}$ of leg	Mid thigh amput. 9*th* day after accident	Recovered	Thrombosis of all veins of amput. specimen	Patent. Active bleeding from proximal end of fem. during amput.
5, Bergendal,[8] 1931	M 33	Unknown	RLE	Phl. caer. dol.	Only fem felt	Foot & lower leg	Leg amput. (36*th* day)	Recovered	Thrombosis of all veins of amput. specimen	Patency of ant. & post. tib., & peroneal. Active bleeding from proximal end of arteries during amput.
6, Bergeret, Guillaume & Delarue,[9] 1932	F 52	Postop. (appendectomy)	RLE	a. Phlebothrombosis b. 9 days later phl. caer. dol.	Absent pedal pulses. Absent oscil. readings	Foot & $\frac{2}{3}$ of leg	Thigh amput.	Died	Thrombosis of all veins of the amput. specimen	Patent. Dissection. distal to fem.
7, Wertheimer & Frieh[10] (Case 1), 1935	M 36	Post i-v infusion.	RUE	Phl. caer. dol. of hand & forearm	Both radial & ulnar felt. Normal oscil. readings	Distal phalanges of last 4 fingers	Amput.	Recovered	—	—
8, Wertheimer & Frieh[10] (Case 2), 1935	M 44	Post i-v infusion	?UE	Cyanosis & motor loss of hand	Absent radial pulse	Hand & lower $\frac{1}{3}$ of forearm	—	Died	Thrombosis of cephalic vein	Patent
9, Carcassonne & Audier,[10a] 1935	F 57	Unknown	RUE	Phl. caer. dol.	All pulses felt	Second finger	Perivascular sympathectomy of brachial vessels	Recovered	Thrombosis of brachial veins	Patent

10, Fontaine, Israel, & Souza Pereira,[12] 1936	M 34	Unknown	RLE	Phl. caer. dol.	Only fem. felt but arteriogram showed patent arteries	Foot	Thigh amput.	Recovered	Thrombosis of all veins distal to com. iliac (operation & dissection of amput. specimen)	Patent. Arteriogram & dissection
11, Gutzeit,[11] 1936	M Child (age?)	Post-traum.	LLE	Phl. caer. dol.	Only fem. felt (popliteal pulsating at operation)	Foot & lower ⅓ of leg	Amput.	Recovered	Thrombosis of all veins of amput. specimen	Patent
12, de Vernejoul, Audier, & Picaud,[42] 1936	M 43	Lung abscess	RLE	Phl. caer dol.	Absent pedal pulses. Normal oscil. read. only above lower ⅓ of leg	Foot	—	Died	Thrombosis of all veins distal to external iliac	Patent
13, Salmon, Audier, Jouve, & Haimovici,[13] 1938	F 50	Heart failure	LLE	a. Phl. a. dol. b. 8 days later phl. caer. dol.	Only fem. felt. Absent oscil. readings	Foot & lower ⅓ of leg	1. Perifem. sympathectomy 2. Leg amput.	Died	Thrombosis of all veins of the amput. specimen	Patent. Arteriogram & dissection
14, Tilley[22] (Case 1), 1938	F 44	Postpartum	RLE	a. Phl. a. dol. b. 3 days later phl. caer. dol.	n.r.	Foot & leg	Thigh amput.	Recovered	Thrombosis of all veins	Patent
15, Tilley (Case 2), 1938	F 38	Postpartum	LLE	a. Phl. a. dol. b. 4 days later phl. caer. dol.	n. r.	Foot	Midleg amput.	Recovered	Thrombosis of all veins	Patent
16, Tilley (Case 3), 1938	F 30	Post-abortum	?LE	a. Phl. a. dol. b. 2 weeks later phl. caer. dol.	n.r.	Foot & leg	Mid-thigh amput.	Died	Thrombosis of all veins distal to com. iliac	Patent. Dissection of amput. specimen & post mortem
17, Pringle[15] (Case 1), 1938	M 60	Post-traum. (foot)	LLE	Cyanosis but no edema. Superficial veins thrombosed	Tib. pulses not felt	Foot & leg	—	Died 6*th* day after accident	Thrombosis of all veins distal to fem.	Patent
18, Pringle[15] (Case 2), 1938	M 37	Post-traum. (wound of axilla)	RUE	Discoloration of ulnar aspect. No edema	Radial not felt. Ulnar n.r.	Hand & forearm	Low arm amput.	Recovered	Brachial ulnar & superficial veins thrombosed. Radial veins patent	Patent. Active bleeding from proximal end of brachial a. during amput.
19, Grégoire,[14b] 1938	F 49	Postop.	LLE	Phl. caer. sine dol.	Only fem. felt. Absent oscil. readings	Foot	Thigh amput.	Recovered	Veins thrombosed. Extent of occlusion n.r.	Patent. Arteriogram
20, Decoulx & Bastien,[19] 1939	F 69	Postop.	LLE	Phl. caer. dol.	Only fem. felt. Absent oscil. readings	Foot & leg	a. Perifem. sympathectomy b. Subsequent thigh amput.	Recovered	Thrombosis of all veins	Patent. Arteriogram & dissection

TABLE 1.—*Continued*

Case Author Date	Sex Age	Etiologic bases	Site of thr-phl.	Clinical aspect of the venous occlusion	Peripheral pulses	Extent of gangrene	Treatment	Result	Anatomic findings of the vessels of the affected extremity	
									Veins	Arteries
21, Favre, Rochet, Frieh, & Godinot,[20] 1940	F 57	Post-traum. & varicose veins	RLE LLE	Phl. caer. dol. bilaterally	Fem. & pedal pulses felt bilaterally	RLE: Ankle (small area of gangrene) LLE: Heel & ankle	RLE: spontaneous recovery LLE: Thigh amput	Recovered	LLE: Thrombosis of all superficial veins. Deep veins patent. Gangrene limited to skin	Patent
22, Gutermuth,[21] 1942	M 45	Ca. of left lung	LUE	Phl. caer. dol.	Wrist pulses felt	Hand	—	Died	Thrombosis of all veins of the entire extremity	Patent
23, Morales-Aparicio[22] (Case 1), 1944	F 30	Post partum	LLE	a. Phl. a. dol. b. 20 days later phl. caer. dol.	n.r.	Foot & lower ⅓ of leg	—	Died. Pulm. emb.?	Thrombosis of all veins	Patent
24, Morales-Aparicio[22] (Case 2), 1944	F 36	Bronchopneumonia	RLE	a. Phl. a. dol. b. 24 hours later phl. caer. dol.	Only fem. felt	Forefoot	Lisfranc amput. of foot	Recovered	No other anatomic findings except pulses felt after subsidence of edema	
25, Fontaine & Forster[30] (Case 1), 1946	M 40	Postop.	RLE LLE	RLE: 15 days postop. phl. a. dol. A few days later: phl. caer. dol. of both lower extremities LLE: 7 days postop. phl. a. dol.	All pulses felt bilaterally. Normal oscil readings	RLE: Foot & lower ⅓ of leg LLE: All toes except 4*th*	Conservative	Recovered	—	—
26, Fontaine & Forster[30] (Case 2), 1946	M 8	Post-traum.	LUE	Phl. caer. dol.	Only brachial felt. Absent oscil readings in forearm	Hand & lower ½ of forearm	Midarm amput.	Recovered	Thrombosis of all veins of amput. specimen	Patent. During amput. brachial was spastic but patent
27, Haimovici & Suffness,[24] 1948	M 62	Postop.	LLE	a. Phl. a. dol. b. 4 days later phl. caer. dol.	All pulses felt. Normal oscil. readings	All 5 toes & 2 plantar areas	—	Spontaneous amput. of toes. Recovered	—	—

Thr. phl. = Thrombophlebitis.
Phl. a. dol. = Phlegmasia alba dolens.
Phl. caer. dol. = Phlegmasia caerulea dolens.
RLE = Right lower extremity.
LLE = Left lower extremity.
RUE = Right upper extremity.
LUE = Left upper extremity.
n.r. = Not recorded.

hind leg. The same year, Wertheimer and co-workers[7] by their investigation on muscular infarction following venous obstruction, shed additional light on the problem of the mechanism of this type of gangrene. In 1938 the foregoing clinical, pathologic, and experimental data were reviewed by Audier and Haimovici.[18] In the decade that followed several more observations were reported.[19–24]

In the American literature the first paper, reporting three cases, was published by Tilley in 1938.[22] Bunn[25]; Meyer[26]; Smith and Quimby[27]; Allen, Barker, and Hines[28]; and Wright[29] apparently have observed similar cases. Unfortunately, these authors did not publish the full account of their clinical and pathologic data. Because of insufficient information, these cases could not be included in our tabulation. Recently (1948), Haimovici and Suffness[24] reported another case and re-emphasized the clinicopathologic characteristics of this type of gangrene.

It appears from this historical review that gangrene of the extremities due to venous occlusion was rarely reported. When compared to the incidence of thrombophlebitis of the extremities, this complication would appear exceptional. It is probable, however, that the syndrome is less infrequent than the literature would lead us to believe. It is my feeling that a certain number of such cases have gone unrecognized because the possibility of gangrene due to venous obstruction alone is not widely known.

The recognition of this complication of thrombophlebitis is, however, of more than academic interest. Indeed, since this type of gangrene is usually superficial or limited to the digits, and since the ultimate tissue loss may not be serious, major amputations might be avoided. It is probable that loss of extremities had occurred because of failure to appreciate this fact.

The rareness of this condition and its possible management by conservative surgical procedures justify a survey of the entire subject. This review is presented with the hope of stimulating further study.

Clinical Manifestations

This study is based on 27 cases, involving 29 extremities (table 1).

The *etiologic* circumstances associated with the cases of thrombophlebitis in this series were the following: postoperative, 5; post-partum, 4; posttraumatic, 6; visceral malignancies, 2; miscellaneous (lung tuberculosis, lung abscess, cardiac decompensation, bronchopneumonia, postintravenous infusion), 6; and unknown, 4.

The *age* of the patients ranged from 8 to 69 years with an average of 41.4 years. The *sex* was almost equally distributed (15 males, 12 females).

The lower extremities were involved in 79.3 per cent of the cases, while in the remaining 20.7 per cent the upper extremities were affected.

The clinical picture of a thrombophlebitis resulting in gangrene is characteristic. The thrombophlebitic process may go through three distinct phases: (1) phlegmasia alba dolens or milk leg, (2) phlegmasia caerulea dolens or blue thrombophlebitis, and (3) gangrene.

1. *Phlegmasia Alba Dolens.*—This phase is well known and needs no further description. It preceded the blue thrombophlebitis by a few days to a couple of weeks in 44 per cent of the cases only. In the remainder of the cases, it failed to appear or may have been overlooked.

2. *Phlegmasia Caerulea Dolens.*—Phlegmasia caerulea dolens, or blue thrombophlebitis, was present as an initial manifestation in 56 per cent of the cases but was seen at a later stage in all instances irrespective of the onset. This phase of the thrombophlebitic process is usually typical in its manifestations.

Edema, considered as the pathognomonic sign of venous occlusion, may be absent at the inception in some cases. But soon thereafter, swelling usually becomes very marked and may extend beyond the groin[5, 8] or the axilla[21]. The main feature is its rapidly progressive development. The skin of the affected limb is glossy, exceedingly tense, and the edematous portion is of a characteristic woody consistency[8]. In a patient with swelling due to cardiac decompensation, phlebitic edema could be easily overlooked, but on closer examination the size of the affected limb is noted to be larger than that of the unaffected limb[13].

Cyanosis was the most characteristic sign. It appeared very early, developed rapidly, and extended to the entire extremity. Its maximum intensity was at the distal parts (toes, heel, fingers) where areas of bluish dark or red discolorations were noted.

Pain was a constant feature which accompanied cyanosis. Its onset may be sudden or pregressive. In the former case it was often mistaken for an embolic pain.[12, 13, 19, 30, 31] Irrespective of its type of onset, this pain was usually more intense than in the common form of thrombophlebitis. Sometimes in patients with

poor general condition, however, pain may go unnoticed[14a].

Local temperature was sometimes normal and it contrasted with the presence of cyanosis. However, in most cases, coolness of the distal parts of the limb was marked. Loss of *motor power* and *hypesthesia*, more frequently than anesthesia, were noted.

Arterial pulses were palpable in one-third of the cases (9 out of 27). In the remaining two-thirds, distal arteries, although patent, could not be felt or their patency was not recorded. It should be borne in mind that the exploration of the pulses in these cases is fraught with difficulties because of the usually excessive edema in the foot, around the ankle, and in the popliteal space. Besides the edema, which may account at least partly for the nonpalpable arteries, the presence of arteriospasm may be another reason for the absent pulses. Suffice it to mention at this point, that in these cases, the patency of all the arteries was verified by careful dissection and also sometimes by arteriography.

Oscillometric exploration of the distal arteries is fraught with the same difficulties as that of the palpation of the pulses. In addition, the application of the cuff is often painful and furthermore may be inadvisable because of possible danger resulting from the pressure on friable venous thrombi. In the cases in which oscillometric readings were taken, the information obtained paralleled that of the pulse findings.

Arteriography, when used[12, 30] revealed the integrity of the arterial tree despite absent pulses and oscillometric readings. This means of exploration is not commonly used, but in such cases might be helpful in identifying the exact nature of the circulatory disturbances.

Multiple venous occlusions involving two or more extremities were not infrequent. In 2 out of the 27 cases, gangrene occurred in both lower extremities. In addition, in 8 out of the 27 cases, concomitant simple uncomplicated thrombophlebitis affecting other extremities was also noted. In one instance[8], the patient had a typical migrating thrombophlebitis the first manifestation of which was that of priapism. Then, in addition to the blue thrombophlebitis and gangrene of the right lower extremity, he developed venous occlusions of the left lower and upper extremities. Gutermuth's case[21] is a similar example of extensive involvement of the venous system (both lower extremities, left upper extremity, and the veins of the neck). The time of appearance of these multiple venous occlusions varied. They rarely appeared simultaneously. In most cases, they either preceded by a few days or weeks the blue thrombophlebitis or followed it from a few days to two months.

3. *Gangrene.*—The course of this type of blue thrombophlebitis was typical. Gangrene of the distal parts of the extremity appeared within four to eight days after the onset of the anoxemic manifestations. It is well to remember, however, that blue thrombophlebitis does not necessarily lead to gangrene. A certain number of such cases, with transient cyanosis and ischemia occurring in the course of thrombophlebitis, have been reported[18, 31–40]. When gangrene occurs, as in the present group, it is in most instances of the "moist" variety, but "dry" necrosis is not incompatible with a venous occlusion[30].

Usually gangrene was limited to the distal parts of the extremities and, most important of all, it remained superficial. The necrotic and surrounding areas presented a characteristic bluish discoloration. Blebs were often noted and lymphangitis also developed. The line of demarcation at the early stage was not always very sharp. If infection accompanied the ischemic disorders of the limb, the latter offered the classical picture of wet gangrene.

Clinical Types

Thrombophlebitis complicated with gangrene can be differentiated into two main clinical types according to the presence of the peripheral pulses: (1) cases with palpable distal arteries and (2) cases with nonpalpable but patent arteries.

The following 2 cases, observed by the author, will best illustrate the two different clinical types.

*Thrombophlebitis Complicated With Gangrene (Distal Arteries Palpable).** M. L., a 62 year old white

* This case was reported in collaboration with G. Suffness.[21]

man, was admitted, on May 26, 1946, to the Alexian Brothers Hospital, Elizabeth, N. J., for neoplasm of the bladder. The patient had had hematuria for about two months prior to his admission. Except for a right inguinal hernia and some degree of chronic bronchitis, the patient's general condition was good. At the time of his admission an electrocardiogram showed no abnormality and the blood pressure was 150/70. On May 27, 1946, a midline suprapubic cystotomy was performed. The tumor was resected and five radon seeds of 1.5 mc. were inserted. The patient was ambulatory forty-eight hours after the operation.

On the fourth postoperative day the patient developed hiccoughs, for which he received carbon dioxide. Three days later congestion of the right lower lobe was diagnosed and confirmed by a roentgen-ray plate exposed on the following day. The patient was running a slight fever (101 F.) but there was no tenderness along the lower extremities. He was given 20,000 units of penicillin every three hours. On June 7 the left calf appeared infiltrated and tense. The diagnosis of thrombophlebitis became apparent. The patient was then given dicumarol (100 mg. the initial dose) and papaverine (½ grain administered subcutaneously every four hours), and his leg was elevated. During the following three days the calf was distinctly tense and the foot was warm. The patient's general condition was good.

On June 11 (fifthteenth postoperative day) at 5 P.M., the patient experienced a sudden pain in the left leg and foot, more marked in the latter. Upon examination, the entire left lower extremity, from the hip down, was found to be swollen. It was also warm, with the exception of the foot and lower third of the leg which were cold and mottled. The circumference at the calf was 38.5 cm. as against 32 cm. on the right side. The dorsalis pedis and the posterior tibial arteries were felt and of good volume. Oscillometric readings were:

	Ankle	Calf
Left	2.5	3.5
Right	2.25	3.5

A paravertebral block with 1 per cent novocain was performed at the first, second, third, and fourth lumbar vertebrae with good immediate results. The severe pain, present before the block, subsided and the patient remained comfortable during the next twenty-four hours. Nevertheless, on the following day, all the toes appeared much more cyanotic than on the previous examination. Another paravertebral block with novocain was performed with immediate good results. Despite that, within the next twenty-four hours, the first and fifth toes appeared completely black, while the second, third, and fourth were black only distally. The areas of gangrene, involving the toes, were most marked on the plantar region. In addition, the ball of the foot and a circumscribed area near the heel also appeared gangrenous (fig. 1). Two days later, another block was performed with the same apparent favorable response. The patient was much more comfortable. A line of demarcation became evident four to five days after the onset of gangrene.

On June 19, the circumference at the calf was 33.5 cm. (5 cm. less than eight days previously). The edema of the entire left lower extremity was subsiding. The areas of gangrene on the plantar region (ball and heel of the foot) showed some fading, while those of the toes remained unchanged).

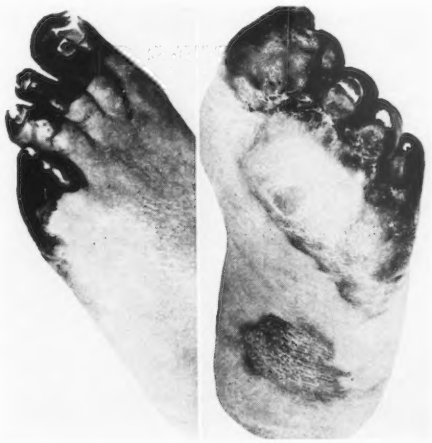

FIG. 1.—Dorsal and plantar regions of left foot. Gangrene involving the five toes, more extensive on the plantar than dorsal surface. Additional superficial necrotic lesions are present on the ball of the foot and near the heel.

On July 1 (three weeks after the onset of the acute ischemic episode) the patient was allowed to be out of bed, and six days later he was discharged from the hospital. His general condition was good. The edema of the lower extremity had completely subsided, and the gangrene of the left five toes was dry and well demarcated. No active surgery was contemplated, for it was assumed that spontaneous amputation would eventually occur. Indeed, the lesions of the ball and heel remained superficial and separated in a few months. As to the toes, after the demarcation between the normal and dead tissues began, the separation of the gangrenous distal phalanges took several months (from Oct. 9, 1946, to Feb. 3, 1947). The stumps (fig. 2) of the different toes were completely healed in May, 1947, eleven months after the onset of gangrene.

While at home, on Sept. 2, 1946, two months after his discharge from the hospital, the patient developed a typical iliofemoral thrombophlebitis of the right lower extremity. The entire limb was markedly swollen, hot, and painful. The patient was running a fever of 101.5 F. The next day a right paravertebral

block was performed and repeated twenty-four hours later. Within twenty-four hours after the last block, the temperature became normal and the pain subsided. The edema of the extremity subsided within a week. Unlike the thrombophlebitis of the left lower extremity, that of the right side was not accompanied by ischemic phenomena and followed a normal course.

When last seen in June, 1947, all pulses were present in both feet and the oscillometric readings were normal. It is to be emphasized that throughout the entire course of the disease the foot arteries remained patent and the oscillometric readings were normal.

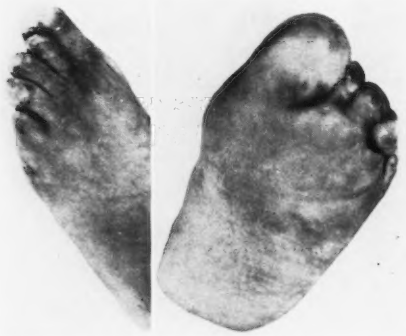

FIG. 2.—The same foot as shown in figure 1. These photographs were taken eleven months after the onset of gangrene. Note the healed stumps of the five toes after spontaneous amputation.

In this case, the clinical course went through four distinct phases. *First phase:* At the inception, during the first few days, the thrombophlebitic process appeared as a typical phlegmasia alba dolens. *Second phase:* On the fifth day the patient experienced a sudden pain and his left leg and foot became cold and cyanotic. The clinical picture took the aspect of a phlegmasia caerulea dolens or blue thrombophlebitis. *Third phase:* Three days later, the toes and two areas of the plantar surface became gangrenous. *Fourth phase:* Regression and demarcation of the lesions began four to five days after the onset of gangrene. The spontaneous amputation of the five toes and the healing of the plantar lesions required several months. At present, there are no postphlebitic sequelae and the walking capacity of the limb is normal. A similar instance in which there was only minimal loss of tissues (spontaneous amputation of the toes) was also reported by Fontaine and Forster[30].

*Thrombophlebitis Simulating Arterial Embolism and Resulting in Gangrene (Distal Arteries not Palpable but Patent).**—The patient, a woman, 50 years of age, with a previous history of several attacks of rheumatic heart disease, was hospitalized for cardiac decompensation. Among other manifestations, she presented edema of both lower extremities, bilateral pleural effusion, reduced diuresis, and allied symptoms.

While in the hospital she had a left iliofemoral thrombophlebitis characterized by pain along the medial aspect of the thigh, hydrarthrosis of the knee joint, and marked edema of the entire extremity.

Eight days later, during the night, she was seized suddenly with a violent pain in the left foot, and cyanosis up to the knee was noted. During the next few hours the pain became excruciating, the cyanosis more prominent, and edema more intense and painful to the touch. These troubles were most marked in the foot. In addition, coldness was also present in the foot and lower half of the leg. Loss of motor power was noted. The femoral artery just below Poupart's ligament could be palpated. None of the other pulses in this limb could be felt. Oscillometric readings were absent below the knee but were obtainable in the thigh. Fifteen to sixteen hours after the onset of this acute vascular occlusion syndrome, surgical exploration, under local anesthesia, of the femoral vessels was performed. The common femoral artery appeared normal; the superficial femoral was reduced in size and was pulsating feebly. However, no clot was present. Stripping of the adventitia over 4 inches released the spasm; the artery resumed its normal diameter and was pulsating freely. (It is noteworthy that as soon as the stripping of the adventitia was completed the patient stated that her pain disappeared). The femoral vein, in its entire length, was distended and filled with a firm clot.

After the operation a paravertebral block with novocain was performed. The leg became warmer but the foot remained cyanotic and cold. After a few days, the general condition grew worse, gangrene of the "wet" type became apparent, and a midleg amputation was performed. At the site of the amputation all the arteries were patent while the veins appeared thrombosed. An arteriogram of the amputated specimen showed a normal arterial tree in the leg and foot (fig. 3). Careful dissection of the vessels revealed that all the veins, large and small alike, were thrombosed. Microscopic examination showed a thrombophlebitic process at some levels, while the arteries appeared quite normal. This patient died a few weeks later from her cardiac decompensation.

* This case was reported in collaboration with Salmon, Audier, and Jouve.[13]

As in the preceding observation, the sequence of events in this case was typical: (1) phlegmasia alba dolens, (b) eight days later, phlegmasia caerulea dolens with acute ischemia and absent distal pulses simulating arterial embolism, (3) after a few days, wet gangrene.

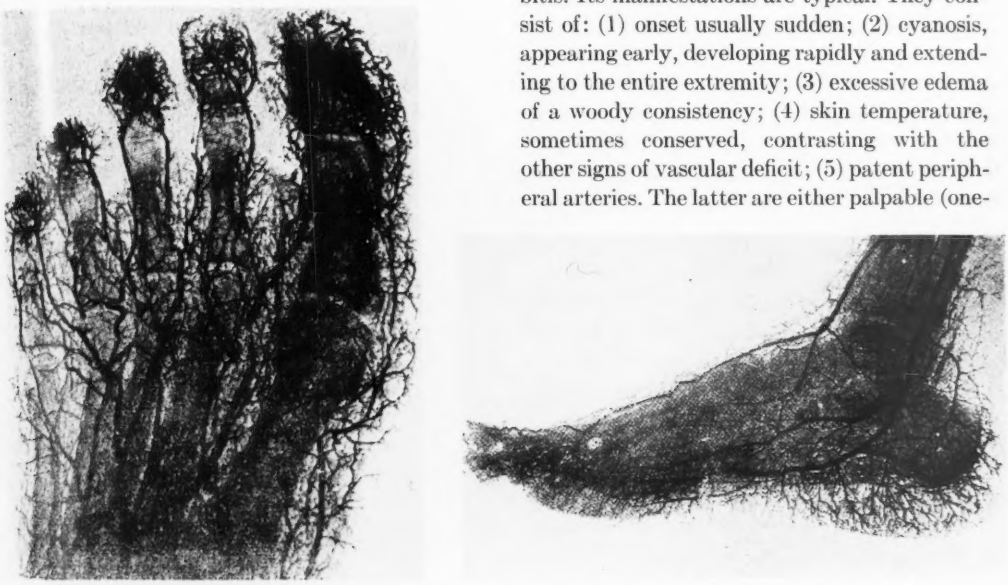

FIG. 3.—Arteriogram of the foot arteries after injection of a minium-turpentine mixture into the arteries of the amputated leg. Both the front and lateral views indicate patency of the entire arterial system. (From Salmon, Audier, Jouve, and Haimovici, Bull. et mém. Soc. de chir. de Marseille, 1938.[13])

This case is a typical example of a thrombophlebitis simulating at its onset a sudden arterial occlusion. A similar pseudoembolic onset was observed in several of the reviewed cases.[14, 19, 30, 41, 42] In my observation the etiologic circumstances and the acute occlusive vascular syndrome made the diagnosis rather difficult. The pathologic findings during the operation and those of the amputated specimen were decisive in establishing the true nature of this case of gangrene.

DIAGNOSIS

Gangrene of venous origin should be suspected whenever a thrombophlebitis is complicated with necrosis. Since this type of gangrene tends to remain superficial, an early diagnosis may be instrumental in avoiding an amputation. To make a diagnosis of gangrene of venous origin, it is necessary to establish the fact that there is thrombophlebitis without arterial occlusion. As already emphasized above, the type of venous occlusion most likely to induce gangrene is the blue thrombophlebitis. Its manifestations are typical. They consist of: (1) onset usually sudden; (2) cyanosis, appearing early, developing rapidly and extending to the entire extremity; (3) excessive edema of a woody consistency; (4) skin temperature, sometimes conserved, contrasting with the other signs of vascular deficit; (5) patent peripheral arteries. The latter are either palpable (one-third of the cases) or their patency is disclosed by an arteriogram or by dissection. When the distal pulses are felt the diagnosis is relatively easy. When the distal arteries are not palpable the diagnosis is difficult or not feasible on the clinical data alone. In the latter instance, other types of occlusive vascular disease should therefore be ruled out.

Differential Diagnosis

Reflex Arteriospasm: Iliofemoral thrombophlebitis associated with a reflex arteriospasm may simulate blue thrombophlebitis.[18, 31–33, 35, 37, 41] The clinical course of the ischemic manifestations in reflex arteriospasm is variable. In some instances the symptoms of local blood-deficiency may disappear spontaneously after several hours and the diagnosis of phlegmasia

alba dolens becomes apparent. In other instances the ischemic phenomena are checked either by the use of papaverine and paravertebral block[37–40] or by periarterial stripping[31]. In all these instances, following these procedures, normal color of the extremity and the distal pulses return. The diagnosis of reflex arteriospasm then becomes evident. Contrasting with the latter cases, in those of blue thrombophlebitis resulting eventually in gangrene, the ischemic manifestations cannot be reversed completely by the above procedures.

Acute Peripheral Circulatory Failure: Acute peripheral circulatory failure caused by acute thrombophlebitis is characterized by loss of pulsations in the arteries of all extremities and should be easy to differentiate if this rare clinical syndrome is kept in mind (Dennis[43] and Morgan and co-workers[44]). In these cases, the arterial pulsations disappear only transiently. Indeed, after proper treatment of the shock, pulses reappear and the diagnosis becomes evident.

Peripheral Arterial Embolism: Blue thrombophlebitis, particularly when associated with severe pain and marked arteriospasm, may closely simulate embolic occlusion.[34] In order to differentiate one condition from the other, the following findings may be helpful. In embolic occlusion, the patient experiences acute pain with blanching of the foot and leg and coldness of the extremity. In such cases, there is usually evidence of a heart condition, either auricular fibrillation or acute coronary thrombosis. In blue thrombophlebitis, the objective findings already mentioned above, that is, enlargement of the extremity, prominence of superficial veins, and the marked cyanosis, should help to distinguish the two conditions. At the inception of the thrombophlebitic process, when edema may be slight, the error might, however, be unavoidable. Indeed, in some cases the nature of the occlusive vascular syndrome has been established only during surgical exploration of the main vessels.[13, 14, 19, 31]

Mixed Arterial and Venous Occlusions: These may present the most difficult problem in the differential diagnosis. Cases of acute thrombophlebitis associated with arterial occlusion (simple arterial thrombosis, thromobangiitis obliterans, or arteriosclerosis obliterans) followed by gangrene may not be easy to distinguish from cases of gangrene due to venous occlusion alone. A previous history of intermittent claudication or a straightforward history of acute arterial occlusion preceding the venous occlusion may be in favor of the diagnosis of mixed arteriovenous occlusive syndrome. However, only careful dissection of the vessels of the affected extremity will reveal the decisive factor.

Among the reported observations of so-called puerperal gangrene,[45–48] a good number appear to be due to mixed arterial and venous obstructions or to the use of ergot. The clinical and particularly the anatomic information accompanying most of such observations is not adequate. It is probable that some of these cases were gangrene of venous origin[46].

Summary

From this review it appears that in some cases the diagnosis may be difficult to establish on the basis of clinical information alone. It is therefore, important to re-emphasize that in these cases the anatomic findings of the vessels of the affected extremity as revealed by a careful post-mortem examination or dissection of the amputated specimen are paramount in establishing the true nature of the gangrene. It is obvious that the patency of the arteries in an amputated limb does not necessarily exclude the possibility of arterial origin of the gangrene because the arterial closure might have been proximal. For this reason, active bleeding from the proximal end of the main artery during the amputation should be an additional criterion in favor of the diagnosis of gangrene of venous origin. In the selection of the cases tabulated in this paper, all these criteria were met.

Pathologic Physiology

Data Supporting the Concept of Gangrene of Venous Origin

Clinicopathologic Data: From the foregoing description, it appears that the prominent features of this clinicopathologic entity consist of a syndrome of venous obstruction associated with gangrene and patency of the arterial tree.

While the clinical data may be very suggestive, however, the main evidence in support of the concept of gangrene of venous origin is furnished by the pathologic findings. Indeed, careful dissection of the entire vascular system (table 1) disclosed an extensive occlusion of the whole venous tree and the absence of any organic lesion of the arterial tree.

Microscopic studies of the involved blood vessels have confirmed the gross findings and offered a rational basis for the understanding of some of the clinical manifestations. From a review of the observations reporting detailed histologic information concerning the blood vessels, it is possible to emphasize the following points of interest.

1. The histologic data on the *venous system* are based on the study of its various segments: femoral, popliteal, anterior and posterior tibials, and muscular and saphenous veins.

The lumen is entirely occupied by a blood clot which is not always homogeneous. At certain points the thrombus is of recent date while at other levels of the venous system the organization of the clot is at an advanced stage. In most cases, the large-sized veins present a recent thrombophlebitic process, with or without a beginning of organization, while the smaller-sized veins present a more advanced process.

The study of the wall of the occluded veins offers evidence of phlebitis of variable intensity. Endophlebitis and interstitial hemorrhagic infiltration are more or less associated and their degree varies with the case and the level of the venous tree. Of special interest to be mentioned is the diffuse inflammatory infiltration of the adventitia. The infiltrative process of this periphlebitis (venous adventicitis) may propagate and extend to the adjacent arterial adventitia. This histopathologic finding is the most probable explanation for the associated arterial spasm which accompanied the thrombophlebitis in some of the cases.

2. *The arterial system* is usually intact. The lumen is empty and the wall appears microscopically normal, with the exception, in some cases of the adventitia. In a case reported by Salmon and his collaborators,[13] a slight degree of adventicitis of the femoral, popliteal, and posterior tibial arteries was noted.

While these anatomic findings suggest a causal relationship between the venous occlusion and gangrene of the extremity, the possibility of gangrene due to venous occlusion *alone* is not readily accepted. In order to understand more clearly the pathogenesis of this type of gangrene, it is important to review briefly some facts regarding the anatomy of the venous system and the data concerning the experimental reproduction of such lesions.

Experimental Data: The anatomy of the collateral channels of the venous system is well known and need not be reviewed. It is, however, pertinent to mention briefly that in both the upper and lower extremities there are two sets of veins, superficial and deep, which anastomose frequently with each other. The ease with which the collateral circulation is re-established, owing to the abundant venous pathways, is one of the main reasons for the absence of anoxemia of the tissues or gangrene in thrombophlebitis.

Indeed, it has long been apparent, both in man and in animals, that simple ligations or even multiple obstructions of the main veins of the limbs induced no important obstacle to the venous circulation. Leriche and Jung[49] and Fontaine and de Souza-Pereira[16] studied in the dog the effects of resection and sclerosing of one or several segments of the venous system (saphenous, femoral, and vena cava). These obstacles to the venous circulation resulted only in a temporary edema not exceeding three to four weeks in duration. Only the division of *all* veins at the root of the hind leg of the dog was followed by gangrene of the limb of the wet type. From their experimental work, Fontaine and de Souza-Pereira concluded: "When the return of the circulation is completely blocked, the resulting stagnation of the venous blood is such that gangrene follows rapidly and the arteriograms are a proof of its pure venous origin."

It appears therefore, from these experimental data, that the completeness of the blockage of the venous return is an essential prerequisite for the occurrence of gangrene. These experimental facts shed interesting light on the ob-

servations made on the pathologic process in human beings.

Pathogenic Mechanism of Gangrene of Venous Origin

Three factors seem to be involved in the pathogenic mechanism of this type of gangrene: circulatory arrest, venous stasis, and vasomotor disturbances.

Role of the Circulatory Arrest: Gangrene as a result of arterial obstruction, regardless of its cause, is ascribed to the interference of blood

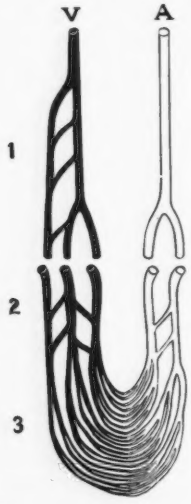

FIG. 4.—Diagram showing the anatomic findings of the blood vessels in an extremity affected by gangrene of venous origin: Occlusion of the whole venous tree (V) including both the deep and superficial main trunks (1), the medium-sized veins (2), and the small branches (3); patency of the whole arterial tree (A).

distribution to the involved areas. In the case of gangrene as a result of venous obstruction alone, blood can apparently reach the tissues. Despite the patency of the arterial system, however, there is circulatory arrest caused by blockage of the return blood flow due to the extensive venous occlusion (fig. 4). In the final analysis it appears that the underlying mechanism of gangrene of venous origin is essentially an obstacle which prevents arterial oxygenated blood from reaching the tissues.

Role of the Venous Stasis: The venous stasis which accompanies the thrombophlebitic process seems to be an important contributing factor to the ischemia. Clinicopathologic and experimental data on infarction of various viscera caused by venous occlusion (gut,[50,53] spleen,[54] kidney[55], brain[56, 57], breast,[58] and of striated muscle[17]) seem to emphasize the role of venostasis in their genesis. Ricker[59] has shown that stasis and anoxemia can be directly responsible for necrosis with hemorrhage. From their work on muscular infarction due to venous occlusion, Wertheimer and associates[17] hold a similar view. In a broader sense, visceral infarcts due solely to venous thrombosis are other illustrations of gangrene obeying the above mechanism.

Role of the Vasomotor Disturbances: On the basis of clinical and experimental evidence, Leriche and Kunlin[60] and Ochsner and DeBakey[36] believe that many of the clinical manifestations in venous thrombosis are due to vasospasm of the arterial and venous systems and that the vasoconstricting impulses originate in the thrombophlebitic segments.

It is not generally appreciated that the veins, like the arteries, respond to many types of stimuli[61]. Malméjac and Haimovici[62] have shown in the dog that stimulation of the lumbar sympathetic chain induces, among other responses, venospasm as expressed in terms of blood stasis and increased volume of the limb.

The role of venospasm in the causation of the circulatory disorders occurring in this type of thrombophlebitis, however, appears difficult to evaluate. It is possible to assume that in some cases it may only contribute to complete the already extensive venous occlusion.

In several of the observations reported in this series, arteriospasm accompanied the thrombophletitis as was definitely established during surgical exploration of the main arteries or as was disclosed by arteriography. In all these instances, the arteriospasm was always preceded by the thrombophlebitic process. On the basis of the available information it is difficult to determine whether or not this spasm extended also to the collateral branches. As to its nature, the histologic evidence presented above points to its reflex origin. Indeed, the propagating adventicitis from the vein to the artery is in favor of this view. Since the presence of arteriospasm accompanying the venous occlu-

sion, in some of these cases, is undeniable, the question arises as to what extent it was responsible for the gangrene. From the available data the arteriospasm appears to play rather a secondary role in its causation. Two sets of facts seem to lend support to this view. First, there are a number of cases of gangrene of venous origin without accompanying arteriospasm. Second, it has been shown experimentally that it can be reproduced by blocking only the entire venous system of the limb. It appears, therefore, that while angiospasm may be an aggravating factor, it is not the initiating cause in the mechanism of this gangrene.

Prognosis

The outcome in the 27 cases, recorded above, leaves much to be desired. Eleven out of the 27 patients died, their general condition being apparently responsible for this poor prognosis. Among the 16 remaining patients, only 3—having 4 involved extremities—had minor gangrene and recovered without surgery. In the other cases, major amputations were performed. It is to be hoped that modern treatment (antispasmodics and anticoagulants) and the knowledge that this type of gangrene usually remains superficial will improve the prognosis.

Treatment

Treatment will vary according to the stage of the clinical manifestations. In the presence of blue thrombophlebitis, the treatment should be directed against: (1) the angiospasm, (2) the propagation of the intravenous clotting, and (3) the underlying condition. There is no need to describe in any detail the different means for the management of these factors. However, it suffices to mention them briefly.

The control of the angiospasm can be obtained by the use of papaverine, Etamon, Priscoline, Dibenamine, or by paravertebral blocks of the sympathetic ganglia with procaine. The latter procedure can be repeated if necessary every twenty-four hours for as many consecutive days as is deemed advisable.[24]

It is generally agreed that anticoagulant therapy is important in the treatment of a sudden vascular occlusion. As indicated above, in the cases of thrombophlebitis followed by gangrene, the entire venous system of the limb was filled with thrombi. Since this event is mainly responsible for the gangrene, it is of the utmost importance to institute anticoagulant therapy (heparin, dicumarol) as soon as possible. The duration of its administration will, of course, be guided by the clinical manifestations.

In addition to the above measures, the treatment of the underlying etiologic condition should also be undertaken concurrently when indicated.

When gangrene sets in, and its venous origin is suspected or definitely established, it is important to bear in mind the fact that these lesions may remain superficial. Gangrene of the deeper tissues may be much less extensive than is apparent from observations of the skin.[24, 29, 30] Amputation should therefore be delayed unless signs of toxemia are present. Antibiotics should prove beneficial under these circumstances. Demarcation of the necrotic areas and their spontaneous elimination may occur.[24, 30] If lesions appear more extensive, a major amputation may become unavoidable.

Summary and Conclusions

A study of 27 cases of gangrene of the extremities following acute thrombophlebitis without arterial occlusion is presented. From the review of the literature it appears that this complication is rare.

The clinical picture of a thrombophlebitis resulting in gangrene is characteristic. Phlegmasia alba dolens, or milk leg, as an initial manifestation was seen in 44 per cent of the cases. Phlegmasia caerulea dolens or blue thrombophlebitis was present in 56 per cent of the cases at the onset but was seen at a later stage in nearly all instances. The latter syndrome is usually typical and consists of edema, often of a wooden consistency, marked and extensive cyanosis, and intense pain. Arterial pulses were palpable in one-third of the cases, while in the remaining two-thirds the distal arteries, although patent, could not be felt to pulsate. In these cases, the exploration of the pulses as well as the oscillometric readings is fraught with difficulties because of the usually excessive edema in the foot around the ankle

and in the popliteal space. Multiple venous occlusions involving two or more extremities were not infrequent (10 out of 27 cases).

The course of this type of blue thrombophlebitis was typical, gangrene of the distal parts of the extremity occurring within four to eight days after the onset of the anoxemic manifestations. In most instances this gangrene is of the "moist" variety, and it usually remains limited and superficial.

The cases can be divided into two main clinical types: (1) thrombophlebitis followed by gangrene with palpable distal arteries; (2) thrombophlebitis simulating arterial embolism and resulting in gangrene with nonpalpable but patent distal arteries. To make a diagnosis of gangrene of venous origin it is necessary to establish the fact that there is thrombophlebitis without arterial occlusion. This condition should be differentiated from: reflex arteriospasm, acute peripheral circulatory failure caused by acute venous thrombosis, peripheral arterial embolism, and mixed arteriovenous occlusions. In some instances the diagnosis can be established only on the basis of the anatomic findings in the vessels of the affected extremity (postmortem examination or dissection of the amputated limb and active bleeding from the proximal end of the main artery during amputation).

From the clinicopathologic and experimental data it appears that the complete blockage of the venous return is the initiating and main cause of this type of gangrene. The angiospasm, when present, may be an aggravating factor, hence its role in the causation of the lesions appears to be secondary. Prognosis depends not only on the degree of the local factors (circulatory arrest, venostasis, and vasomotor disturbances), but also on the underlying etiologic condition. The latter is mainly responsible for the poor prognosis as to life. Management by conservative surgical procedures should always be attempted except in the cases of extension of the lesions and the presence of signs of toxemia.

Addendum

Since this article was submitted for publication, another cases of gangrene of venous origin came under my observation. The patient, a woman 42 years of age, was hospitalized at Montefiore Hospital for paraplegia due to intramedullary cord tumor. During her stay at the hospital she had several operations. On February 1, 1949, a few days after a laparotomy, both lower extremities became cyanotic and markedly edematous, and the right foot and lower third of the leg became gangrenous. Only the femoral pulse was felt. The patient died seven days later. On postmortem examination, an arteriogram and the dissection of the vascular system revealed patency of the entire arterial tree and thrombosis of the venous tree from the vena cava inferior down to the toes.

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Mechanism of the Auricular Arrhythmias

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The four auricular arrhythmias, premature systoles, paroxysmal tachycardia, flutter, and fibrillation, have been investigated in over 200 dogs by three methods: (1) high speed cinematography, (2) cathode-ray oscillography, and (3) multiple-channel electrocardiography. The hitherto unexplored body of the left auricle has been surgically exposed and thoroughly studied. Results indicate that all four arrhythmias are of unitary origin and may occur from one ectopic focus. The resulting arrhythmia depends largely upon the rate of discharge from that focus. There is no circus movement. Corroborative observations have been made on the arrhythmias in man. This conception of the auricular arrhythmias simplifies the understanding of their mechanism.

SINCE the classic studies of Lewis and his associates[1] on the nature of the auricular arrhythmias, comparatively little has been published on this phase of the subject. Lewis believed that his experiments established the following concepts concerning the mechanisms of the auricular arrhythmias:

1. That auricular flutter is due to a regular circus movement in the auricles which sweeps around the openings of the venae cavae. The main impulse usually travels in a counterclockwise direction up the right auricle, circling the superior vena cava, then down the left auricle, and around the inferior vena cava, thus completing the circus. Regular daughter waves are sent off the main wave to the remainder of the auricles.

2. Auricular fibrillation is due to a circus movement of the same general type as that of auricular flutter, but in this instance the impulse pursues a tortuous and redundant path around the venae cavae and sends off irregular daughter waves to the remainder of the auricles.

3. Paroxysmal auricular tachycardia is of a different nature. Lewis believed that a rapidly discharging ectopic focus in the auricle is responsible for the arrhythmia; no circus movement is present. Other investigators, however, do favor circus movement as the mechanism of auricular tachycardia.

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The evidence that Lewis gathered with regard to circus movement appeared so complete that his conclusions have been accepted as fact in most modern textbooks of physiology, cardiology, and medicine.

For the past three years we have been taking high-speed, colored cinematographs of the auricles of the intact dog's heart. A Western Electric Fastax 16-mm. camera was used with which films were taken at speeds up to 2,000 frames per second. When films taken at 2,000 frames per second are projected at eight frames per second the motion of the auricles is slowed 250 times. Auricular events that occur in one second take four minutes to view on the screen. A magnifying lens is used which enlarges the auricle 100 or more times on projection. By careful photographic technic, and lighting the field with twelve RSP-2 photospot incandescent lamps, excellent pictures are obtained showing the most minute detail of auricular activity. By means of such pictures, the *auricular contraction wave can actually be seen* for the first time.

We have now studied over 75,000 feet of film from experiments on over 200 dogs with various experimentally induced auricular arrhythmias. The arrhythmias were produced by the aconitine[2,3] and by the postelectrical stimulation methods. Simultaneous electrocardiograms were taken in all experiments. The electrocardiographic studies were usually done by means of a Technicon Cardiograph, a direct writing machine, which records three leads simultaneously. It is thus possible to make immediate and accurate observations upon the intrinsic deflections inscribed simultaneously

by two or three electrodes placed on the auricles at strategic points, and at known distances from a firing focus. Thus, small differences in time of arrival of the cardiac impulse beneath each electrode can be accurately determined and the exact direction as well as the speed of the impulse can be definitely established. A dual-beam, cathode-ray oscillograph was employed in a number of experiments. This apparatus is especially valuable because (1) the electrical events at two points can be investigated simultaneously, (2) mechanical resistance is completely eliminated, and (3) the degree of amplification in time and magnitude of the impulse is much greater than that of standard equipment.

Auricular Fibrillation

Motion Picture Observations: In the motion pictures, auricular fibrillation is characterized by two phenomena: (1) Minute irregular contractions that are *continuously* present; these we term M contractions. (2) Large rhythmic, wavelike contractions; these we term L contractions.

The M contractions cannot be seen with the unaided eye, but reveal themselves on the high-speed films. They occur constantly throughout the auricular musculature and involve an area of auricular wall approximately .03 to 3 mm. in diameter. Superimposed on this sea of small contractions are large, moderately vigorous contractions that sweep across the auricle in a fairly regular wavelike manner, at rates of about 400 to 600 per minute. The "fibrillation" of the auricle that is visible to the unaided eye is due to these large contractions. These contractions are fairly uniform in time, but not in strength. They *do not pursue a circus path*, and *no daughter waves are seen on the films*. It can be stated that careful visual investigation by slow-motion pictures of both auricles, individually and together, provide conclusive evidence against circus movement in auricular fibrillation.

A variety of specific experiments designed to block the hypothetical circus path (burning, cutting, and the like) has been performed. These experiments have confirmed the visual evidence for the absence of circus movement.

Electrocardiographic Studies: We have investigated the electrical activity in auricular fibrillation by the electrocardiographic and oscillographic methods described above. In the ordinary electrocardiogram the familiar "f" waves probably represent the L contractions. In direct auricular leads small, rapid, irregular deflections are also present. These small waves of electrical activity may be related to the M contractions seen on the motion pictures, and are therefore also termed M waves. On the ordinary direct-lead electrocardiogram the M waves number roughly 800 to 1,600 per minute; on the more sensitive oscillogram they number as high as 10,000 to 40,000 per minute. The M waves are seen only in auricular fibrillation and indirect evidence has been obtained which indicates that these small, irregular waves are largely responsible for the irregular ventricular responses characteristic of this arrhythmia. In ordinary electrocardiograms of auricular fibrillation, the M waves cause tiny, rough irregularities in the "f" waves. The M waves are not present in the auricular waves of other rhythms.

Simultaneous records from two closely adjacent unipolar electrodes placed at numerous selected points on the auricular surfaces show that all waves are arrhythmic and are usually unrelated in frequency or amplitude. There is no evidence of a circus movement.

Oscillographic records made through esophageal leads in man with auricular fibrillation demonstrate electrical activity similar to that found in the experimental animal.

It was shown that digitalis greatly reduces both the amplitude and frequency of all types of electrical activity in the fibrillating auricles. The decreased electrical bombardment of the auriculo-ventricular node offers an explanation for the decreased ventricular rate in auricular fibrillation after digitalis administration.

It is concluded that in both man and animals, auricular fibrillation is a chaotic heterorhythmic disturbance. There is no circus movement.

Auricular Flutter

Motion Picture Observations: Auricular flutter is due to regularly recurring contraction waves

discharged from an ectopic focus at such a rapid rate that varying degrees of A-V block are produced. The flutter waves are similar to the large waves seen in auricular fibrillation but are more regular and generally more vigorous. No M contractions are seen in auricular flutter. No circus movement exists. Our evidence is as follows:

1. No circus movement of the wave of contraction in auricular flutter can be seen in the films. No daughter waves are present.

2. Interruption of the Lewis circus pathway, by burning or cutting, does not in any way interfere with the auricular flutter, either photographically or electrocardiographically.

3. Slow-motion pictures were taken of both auricles simultaneously during auricular flutter. The films were projected so that motion was slowed 250 times. If a circus movement were present, at rates of conduction as calculated by Lewis, on films taken at this speed one appendix should be seen to contract many seconds before the other. However, it can be clearly seen on the films that both appendices contract at nearly the same instant.

4. When auricular flutter is produced by applying aconitine locally at the center of the wall of the right auricle, the contraction waves are seen to originate at the ectopic focus in a perfectly rhythmic manner, and to spread over the auricles in *all* directions at once. It thus appears clear that the mechanism of auricular flutter is not a circus movement; for if it were, the contraction wave would have to pursue a unidirectional path around the cavae. The films show that this is not the case; each contraction wave takes its origin at the ectopic focus, and, instead of traversing the auricle in a single direction, actually spreads from the focus simultaneously in all directions. The visual observations disprove the circus movement theory of auricular flutter and establish the true nature of this auricular arrhythmia.

Electrocardiographic Studies: Lewis's evidence for circus movement in flutter is based on timing the intrinsic deflections with paired auricular electrodes. By the technic in general use at that time, the body of the left auricle could not be exposed sufficiently to allow adequate electrographic investigation in that region. As a result, a considerable gap in Lewis's hypothetical circus path exists. Since we have been able to obtain wide exposure of the body of the left auricle, it seemed advisable to analyze the intrinsic deflections in *both* auricles, including the heretofore unexplored gap (the body of the left auricle), and thus test our cinematographic conclusions by Lewis's own method.

By means of extensive dissection, we have explored both auricles, including the body of the left auricle, in 30 dogs, with completely consistent results, as described in the following experiments.

Experiment 1: Aconitine was placed in the natural crevice between the inferior vena cava and the pulmonary vein from the left lower lobe. This point approximates the caudal attachment of the interauricular septum to the wall of the auricles. Electrodes were placed equidistant (2 cm.) from the aconitine focus, one electrode on the body of each auricle respectively.

If a circus movement is present, the impulse should arrive at the electrode of one auricle an appreciable time (at least 0.15 second) before it reaches the other. We have found that this was not the case; the impulse arrived at both electrodes nearly simultaneously (within 0.005 second).

Experiment 2: Aconitine was placed at the same point as in Experiment 1. Paired fixed electrodes were placed on the body of the right auricle—one at a point 1 cm. from the aconitine focus, the other at a point 4 cm. from the focus. We have found that the impulse arrived at the more distal electrode at a significantly later time than at the proximal electrode.

The same procedure was now repeated on the left auricle in the same animal. The paired electrodes were transferred to analagous positions on the body of the left auricle. The timing of the respective intrinsic deflections clearly demonstrated that the course of the impulse in the left auricle was in the same direction as in the right, i.e., *away from* the aconitine focus.

This finding is of crucial importance since, if the impulse were pursuing Lewis's circus path, it should on its "return journey" travel *toward* the aconitine focus instead of *away from* it.

Thus, by Lewis's own method, when the course of the impulse over the heretofore unexplored gap (body of left auricle) is charted, the circus movement theory is shown to be invalid and the true nature of flutter is revealed.

Experiment 3: As described for the similar motion-picture experiment, aconitine was placed in the center of the body of the right auricle. After flutter

was produced, an electrode was placed on each side of the focus and equidistant from it.

It was found again that the impulse arrived at each electrode simultaneously.

The observations of this experiment confirmed those seen on the motion-picture and in the other electrocardiographic experiments that the impulse travels away from the focus into all directions simultaneously.

The configuration of the auricular flutter wave of the electrocardiogram has been elucidated by these studies. It is found to consist of a P′ wave followed by an oppositely directed, prominent Ta wave. The Ta wave also occurs in rapid paroxysmal auricular tachycardias. These observations on the configuration of the auricular complex have been found to be true in both animals and man.

These observations on the mechanism of flutter have been confirmed in the human. It has been found that there is an intrinsic deflection in esophageal and precordial leads in patients with auricular flutter. By timing the intrinsic deflection and observing the general configuration of the auricular complex, ectopic foci have been demonstrated in humans with flutter. The ectopic focus is characterized by a completely negative deflection. As the impulse travels away from this focus, the intrinsic deflection is preceded by a positive component which becomes larger as the distance from the focus is increased. Utilizing both the configuration of the auricular deflection and the timing of the intrinsic deflection, it has been found that the impulse spreads concentrically from the ectopic focus. There is no circus movement.

Auricular Tachycardia

Films of paroxysmal auricular tachycardia and of auricular flutter reveal that the contraction waves in the two rhythms are similar. The two arrhythmias differ in at least three respects: (1) The auricular rate (the rate of discharge from the ectopic focus) in tachycardia is slower than in flutter. (2) As a result of this slower rate each auricular wave is followed by a ventricular response, that is, no A-V block exists in auricular tachycardia. (3) The propagation of the individual tachycardia wave is faster than that of the flutter wave. As in flutter, each tachycardia contraction wave originates in an ectopic focus in the auricular musculature and proceeds to invade the auricles in all directions simultaneously.

Unitary Nature of the Auricular Arrhythmias

From our cinematographic, electrocardiographic and oscillographic observations the same basic mechanism would appear to be responsible for auricular premature systoles, auricular paroxysmal tachycardia, auricular flutter, and auricular fibrillation, that is, *a single ectopic focus.*

Evidence in favor of this viewpoint can be obtained from the following experiment, using a modification of Scherf's aconitine method.[3] A drop of a 0.2 per cent solution of aconitine in benzene is placed on a small area (swabbed dry) of the wall of the auricle. Auricular fibrillation usually results after a few minutes. When the ectopic focus is cooled by spraying with ethyl chloride, the rhythm often changes in the following order: from auricular fibrillation to auricular flutter, auricular tachycardia, and sinus rhythm with auricular premature systoles. When the cooling is stopped and the point of application of the aconitine is allowed to come towards body temperature, a return of the arrhythmias in reverse order is usually observed. By manipulating the amount of aconitine applied and/or the temperature of the focus, it is often possible to maintain any desired arrhythmia for a relatively long period of time. Study of the slow-motion picture films of these experiments reveals that the contraction waves in auricular premature systoles, auricular tachycardia, and auricular flutter are indistinguishable except for their rate and speed of conduction. When the rate of discharge of impulses from an ectopic focus exceeds a certain critical level varying from 300 to 600 per minute in different animals, auricular flutter gives way to auricular fibrillation.

The same sequence of auricular arrhythmias as described above may be produced by electrical stimulation instead of the local application of aconitine. The rate of discharge of impulses can thus be controlled at will. As the rate is increased from 100 to 600 stimuli per minute, it is often possible to produce the cinematographic

appearance of auricular premature systoles, auricular tachycardia, auricular flutter, and auricular fibrillation in the order named. The arrhythmias produced by electrical stimulation appear identical photographically with those produced by aconitine.

It is noteworthy that the same close relationship and transitions described above for the experimentally produced auricular arrhythmias have also been frequently observed in man, spontaneously, and after medication, after certain surgical procedures, after trauma to the heart, and following certain infections.

The present conception of the action of antiarrhythmic drugs, such as quinidine and digitalis, is that they act largely through their supposed effect on the gap between the head and the tail of the circus movement. In the light of the above observations such a concept is untenable.

The observations on the auricular arrhythmias described in this paper will be included in a monograph now in preparation which will cover the entire subject in full detail.

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Subendocardial Infarction: Report of Six Cases and Critical Survey of the Literature

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In the ordinary evolution of an acute myocardial infarct the electrocardiogram shows T wave (ischemia), RS-T segment ("current of injury") and QRS (death of muscle) changes. This paper presents a special group of cases of infarction in which only T wave and RS-T segment changes developed even when patients were observed over a considerable period. Therefore, the curves as such could not be considered diagnostic of myocardial infarction. The authors here describe a unique and intriguing group of cases of fatal myocardial infarction with electrocardiograms resembling those seen in stress tests for coronary insufficiency and showing rimlike subendocardial infarcts at postmortem.

IT IS now quite generally recognized that acute transmural infarcts of circumscribed distribution and resulting from inadequacy of the flow of blood through one of the major coronary branches may be accurately detected and localized electrocardiographically. Initially these were regarded either as anteroapical or posterobasal in distribution, but with the development of the multiple chest lead technic and unipolar electrocardiography it has become possible to recognize anteroseptal, anterolateral, posteroseptal, and similarly located infarcts. It is also known that, classically, these zonal transmural infarcts are roughly wedge-shaped with the base of the wedge toward the endocardium. Recent isolated studies,[1–6] however, have demonstrated the feasibility of recognizing myocardial infarcts which are principally limited in distribution to the subendocardial layers of the myocardium.

In the investigation of 150 consecutive individuals who were studied at least once during their terminal illnesses by means of a multiple unipolar electrocardiographic technic, and who were subsequently examined post mortem,[7] 6 individuals were found with infarction of this type among 65 with myocardial infarction. It is the purpose of this article to present this group of 6 cases of subendocardial infarction confirmed at autopsy and to discuss the relevant literature.

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The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the Naval service at large.

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CASE REPORTS

Case 1. (P.B.B.H., 7A850). S.L., a 53 year old shipper with syphilis and angina pectoris, was admitted to the Peter Bent Brigham Hospital on March 15, 1948, because of severe substernal pain of four days' duration. Physical examination showed the patient to be in shock with a heart rate of 104 and an unobtainable blood pressure. The electrocardiogram (fig. 1, *A*) showed depression of the RS-T segments in Leads I, II, aV_F, V_4, V_5, and V_6 and elevation of the RS-T segments in Leads aV_R and V_1 to V_3; there was no Q wave in Leads III or aV_F. These tracings were interpreted as very suggestive of subendocardial infarction of the left ventricle. The patient died three hours after admission to the hospital.

Postmortem examination showed the characteristic findings of syphilitic aortitis with marked narrowing of the coronary ostia. Except for a few small yellowish plaques, the coronary arteries were normal. The heart weighed 380 grams, was removed in toto, and fixed. Following fixation in formalin it was sectioned transversely at 1-cm. intervals from the apex to the atrioventricular sulcus. This technic was used in all but one of the cases described in this article. In cross section (fig. 1, *B*) the wall of the left ventricle was seen to consist of three concentric layers. The outer (subepicardial) layer consisted of normal-appearing myocardium. The second, middle layer, consisted of pale, firm myocardium averaging 1.2 cm. in thickness. Both of these layers appeared normal microscopically. The pallor can be accounted for by fixation artifact. The inner (subendocardial) layer, measuring 0.2 cm. in thickness, was purple in color and of a soft consistency. This layer demonstrated the changes of myocardial infarction of seventy-two to ninety-six hours' duration

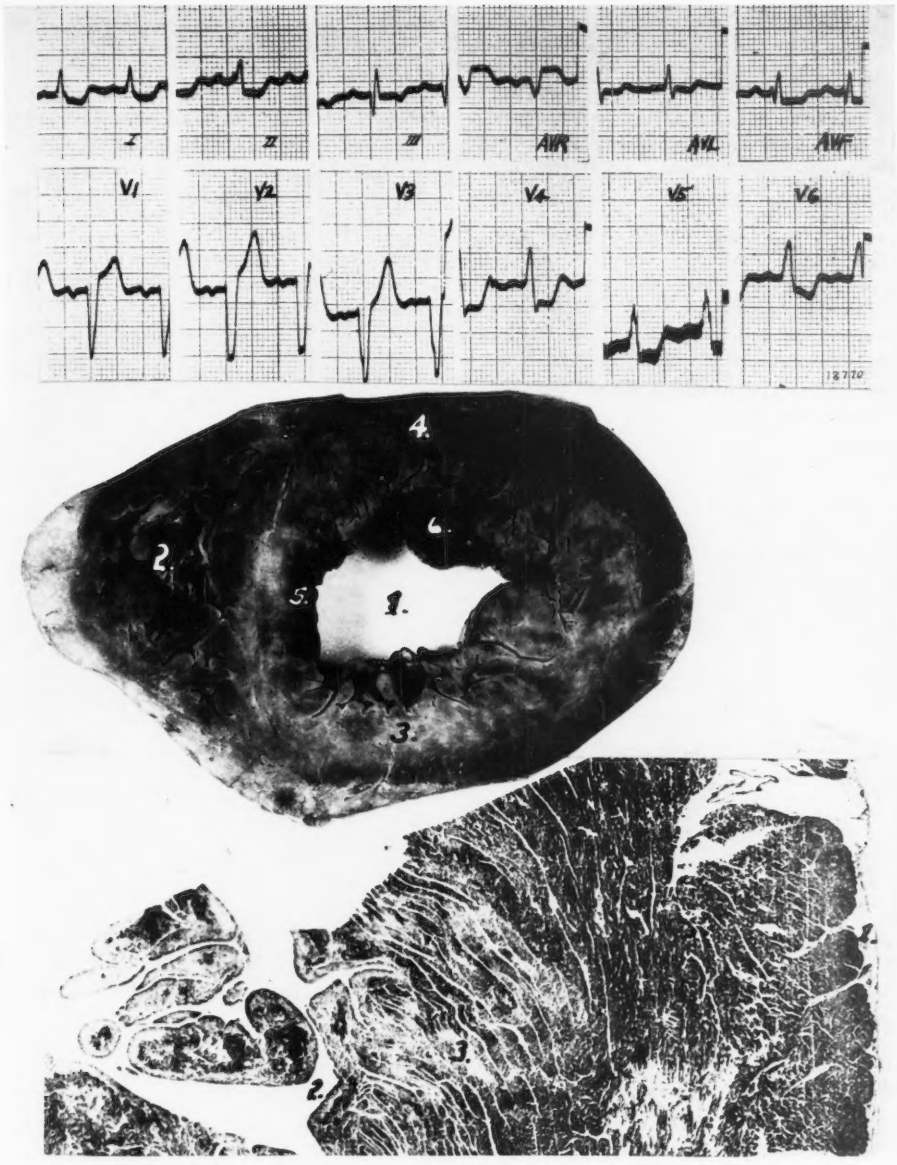

FIG. 1.—Subendocardial Infarction with Syphilitic Ostial Disease (Case 1).

A, Tracing shows depression of RS–T segments in Leads I, II, aV_L, aV_F, and V_4 to V_6; elevated RS–T segment and late inversion of the T wave in aV_R suggest injury orientated toward the ventricular cavity. The depressed RS–T segments in V_4 to V_6 suggest either subendocardial infarction or transmural posterior infarct but the latter is unlikely because of the absence of a Q wave in Lead aV_F. *B*, Transverse section of the heart between the apex and the atrioventricular sulcus (midway). Note the subendocardial rim of dark, infarcted muscle corresponding to the distribution of the subendocardial portions of the superficial sino- and bulbospiral muscles. The posterior papillary muscle is also infarcted. (*1*, Left ventricle; *2*, right ventricle; *3*, anterior; *4*, posterior; *5*, infarcted zone; *6*, infarcted posterior papillary muscle.) *C*, Low-power photomicrograph of myocardium showing pale rim of normal-appearing myocardium separating the endocardium from the infarcted area and sheathing the infarcted trabeculae carnae. Note small patent coronary vessel in the epicardial fat. (*1*, Epicardium; *2*, endocardium; *3*, infarcted zone.)

according to the criteria of Mallory and associates.[8] Further microscopic examination (fig. 1, *C*) revealed a zone of relatively intact myocardium, 0.5 mm. thick, immediately beneath the endocardium separating it from the infarcted myocardium. The infarcted area extended from the base to a point midway from the apex and was most extensive at a point 5 cm. from the apex.

In this case the upward RS–T displacement in leads from the right side of the precordium and the downward displacement in the leads from the left side would also be consistent with anteroseptal infarction. It is possible that, had the patient lived longer, he might also have developed QRS changes. The lack of distinct QRS changes might also be explained as the result of subendocardial infarction, particularly if prolonged electrocardiographic observation fails to reveal the development of QRS changes while collateral clinical evidence of infarction is present. In the patient of Alzamora,[6] almost duplicate conditions existed. Each had syphilitic narrowing of the coronary ostia, each showed a similar unipolar electrocardiographic pattern (depression of the RS–T segment over the precordium, elevation of RS–T in aV_R, and no significant Q wave in aV_F) and each showed infarction limited to the subendocardial strata. The patient with subendocardial infarction reported by Pirani and Schlichter,[5] who had narrowing of the coronary ostia by calcific plaques and a positive serologic reaction for syphilis, almost certainly belongs in the category with these two cases. The electrocardiogram of this patient, employing CF leads, showed depression of the RS–T segment in Leads I, II, CF_4 and CF_5 which was considered characteristic of so-called left ventricular strain.

Case 2. (P.B.B.H., 7A918). E.L., a 58 year old housewife with long-standing diabetes mellitus, arteriosclerotic heart disease, and congestive heart failure, was admitted to the hospital while suffering an attack of myocardial infarction. Physical examination showed the patient to be in shock, with tachypnea (respirations 40 to the minute). Her skin was ashen-gray in color. The electrocardiogram (fig. 2, *A*) showed a prominent S wave, depressed RS-T segment, and biphasic T wave in Lead I; a depressed RS-T segment and inverted T wave in Lead II; and a T wave in Lead III which was low and biphasic. The unipolar limb leads showed an elevated RS-T segment with upright T wave in aV_R, depressed RS-T segment and biphasic T wave in aV_L, and absence of a prominent Q wave in aV_F. The unipolar chest leads showed slight depression of the RS-T segments in Leads V_4 and V_5, biphasic T waves in V_4 and V_5, and inverted T wave in V_6; the transitional zone was between V_3 and V_4. These tracings were interpreted as consistent with acute cor pulmonale; subendocardial infarction was considered but thought less likely. Tracings on the following day showed no further change. The patient died three days later.

Postmortem examination showed cardiac enlargement (the heart weighed 650 grams) and severe coronary sclerosis, but no fresh thrombus was found. The heart was fixed and sectioned in the manner described for Case 1. The endocardial half of the posterior wall of the left ventricle showed purple laminations which extended well to the posterolateral angle and to the posterior half of the interventricular septum; there were small focal patches of similar discoloration in the endocardial one-third and papillary muscles of the anterior wall of the left ventricle, best seen near the apex (fig. 2, *B*). Microscopic examination showed these areas to exhibit the features of a three-week old infarction with a normal-appearing zone of myocardium 0.3 mm. thick immediately beneath the endocardium. There was no pulmonary embolism or infarction.

In this case the electrocardiographic diagnosis of acute cor pulmonale was favored over that of subendocardial infarction although the latter was considered. Master and his collaborators[9] described a case which is quite the reverse, that is, one in which the tracing resembled subendocardial infarction but in which acute cor pulmonale was found at autopsy. Büchner[10] described coronary insufficiency with focal necrosis distributed under the endocardium of the right ventricle resulting from pathologic overloading of the right ventricle produced in experimental pulmonary embolism. There is good evidence for impairment of coronary blood flow in acute cor pulmonale but at present it is not known with certainty which part of the myocardium suffers most from this impairment. Insofar as right ventricular pressure is raised, one might expect a decrease in the blood supply to the right ventricle but this wall is thinner, its arteries enter the muscle on a straighter course than do those entering the left ventricle, and the deeper layers are closer to their nutrient vessels.[1] It seems possible, therefore, that acute cor pulmonale and

subendocardial ischemia or infarction are not necessarily incompatible conditions and may at times coexist. At present adequate data to answer this question are not available and we can merely propose the problem.

Leads I and II. The unipolar limb leads showed depression of the RS-T segment in aV_L and biphasic T waves in aV_L and aV_F. The unipolar chest leads showed tall R waves, depressed RS-T segments, and inverted T waves in V_5 and V_6 with slight elevation of the RS-T segments in V_1 and V_2. There

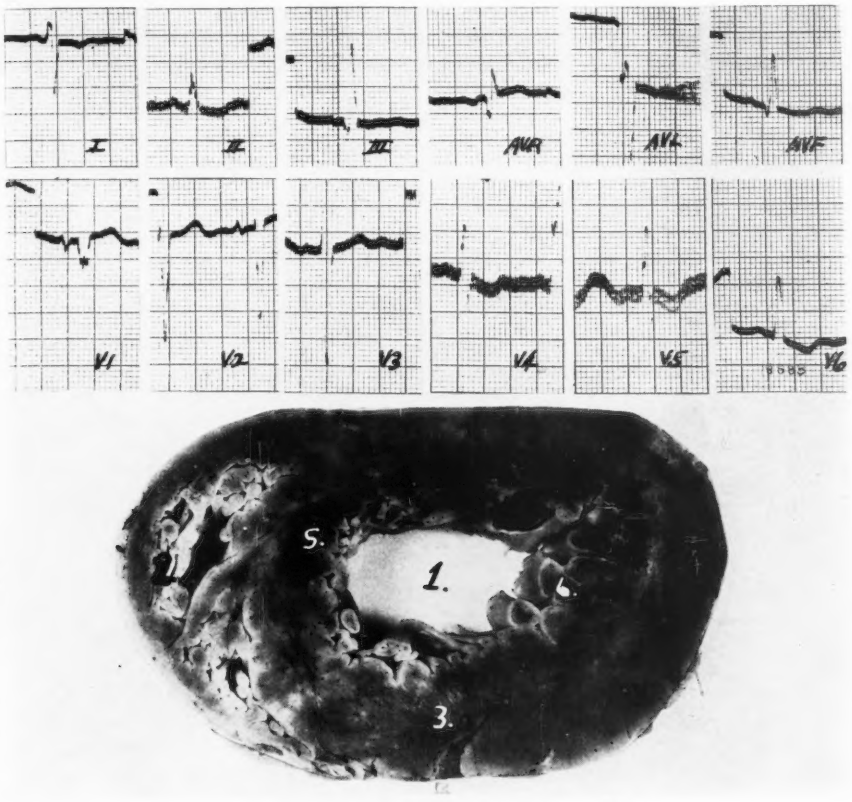

FIG. 2.—Subendocardial Infarction Resembling Acute Cor Pulmonale (Case 2).

A, Tracings show a prominent S wave, depressed RS–T segment, and biphasic T wave in Lead I; depressed RS–T segment and inverted T wave in Lead II; low biphasic T wave in Lead III; elevated RS–T segment and upright T wave in Lead aV_R; biphasic T wave in aV_L; slightly depressed RS–T segment in V_4 and V_5. The Q wave is present but not prominent in aV_F.

B, Transverse section of lower half of the heart showing a circumferential rim of infarcted myocardium, most prominent posteriorly, involving papillary muscles. (*1*, Left ventricle; *2*, right ventricle; *3*, anterior; *4*, posterior; *5*, infarcted zone; *6*, infarcted columnae carnae.)

Case 3. (P.B.B.H. 179739). A.P., a 61 year old piano-maker with pernicious anemia, was admitted to the hospital because of an attack of myocardial infarction. On admission his blood pressure was 146/80. The electrocardiogram (fig. 3, *A*) made eighteen hours after admission, showed an abnormal form of the ventricular complex with slight depression of the RS-T segments and biphasic T waves in were frequent ventricular premature beats and auricular premature beats. These changes were interpreted as characteristic of left ventricular hypertrophy. The patient died on the following morning. A second electrocardiogram had not been made.

The significant findings at postmortem examination were limited to the heart. This organ weighed 440 grams and showed thickening of the left ven-

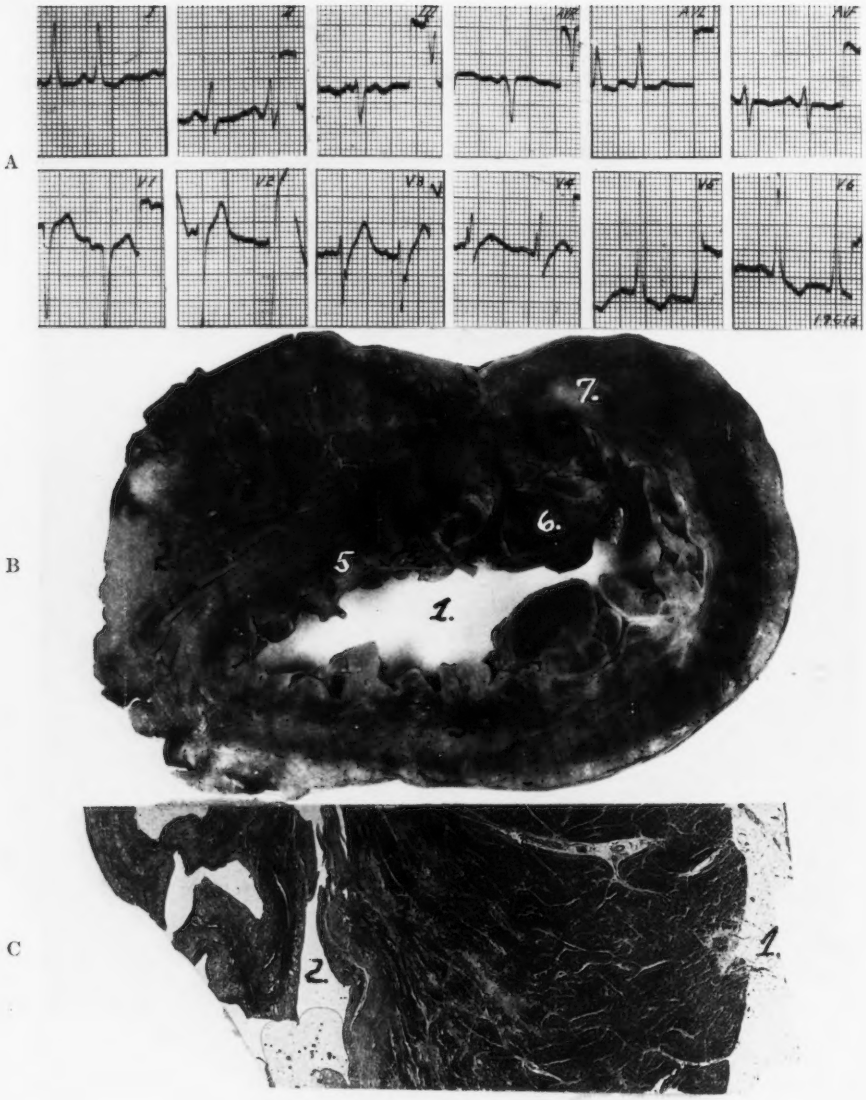

FIG. 3.—Left Ventricular Hypertrophy Possibly Masking the Electrocardiographic Evidence of Subendocardial Infarction (Case 3).

A, The tracings show depressed RS–T segment in Lead I, left axis deviation, depressed RS–T segment in aV_L, biphasic T wave in aV_L, elevated RS–T segment in V_1 to V_3, tall R wave in V_5 and V_6,—features characteristic of left ventricular hypertrophy. No superimposed changes suggested infarction. (These tracings may not have been made at the time of the terminal infarction.) *B*, Transverse section through ventricles. Note old posterior scar extending laterally. There is a purple rim of infarcted myocardium extending around the entire circumference of the left ventricle confined to the inner one-third of the left ventricular wall and involving the papillary muscles. (*1*, Left ventricle; *2*, right ventricle; *3*, anterior; *4*, posterior; *5*, infarcted zone; *6*, infarcted posterior papillary muscle; *7*, old posterior scar.) *C*, Low-power photomicrograph showing dense scarring immediately subendocardial and the subjacent patchy necrosis limited to the inner one-third of the thickness of the wall. (*1*, Epicardium; *2*, endocardium; *3*, infarcted zone beneath scarred area.)

tricular wall. The coronary arteries were markedly sclerotic throughout with striking reduction of caliber of the lumen but no antemortem thrombus was seen. The heart was sectioned as previously described. The posterior wall of the left ventricle was the site of an old white myocardial scar which was transmural in distribution and which extended around the left lateral aspect of the left ventricle with a subendocardial distribution (fig. 3, *B*). In addition, a rim of left ventricular muscle next to the endocardium varying in width from 1 to 3 mm. was the site of purplish discoloration; similar areas were seen in the papillary muscles of the left ventricle. These changes were circumferential involving the nonfibrotic portion of the myocardium. Microscopy (fig. 3, *C*) showed the white areas to be healed myocardial infarction which was transmural and the purple areas to be subendocardial areas of acute infarction of less than twenty-four hours' duration.

In this case the electrocardiogram showed changes of left ventricular hypertrophy while autopsy showed an old posterior myocardial infarction and a very recent subendocardial infarction. Autopsy experience[7] has shown that old posterior myocardial infarction may very easily be missed electrocardiographically especially in the presence of left ventricular hypertrophy. Since depression of the RS–T segments over the left precordium occurs in left ventricular hypertrophy it would be conceivable that the superimposed development of fresh subendocardial infarction might be missed because the electrocardiogram had already shown RS–T depression. However, since the tracings were made more than twelve hours before exitus, it seems possible that, had tracings been made during the two hours ante mortem, changes of subendocardial infarction might have been revealed. Nonetheless, it would seem that, in some cases, the changes of acute subendocardial infarction may be masked by pre-existent left ventricular hypertrophy. A similar situation was noted in Case 5 (below) and in the case described by Pirani and Schlichter.[5]

Case 4. (P.B.B.H., 8A459). A.A.C., a 48 year old manufacturer, with a history of angina pectoris and one attack of myocardial infarction three years previously, was admitted to the hospital because of a fresh attack of infarction associated with syncope. The electrocardiogram (fig. 4, *A*) showed complete A-V block with an auricular rate of 94 and a ventricular rate of 42 beats to the minute. There was marked depression of the RS-T segments in Leads I, aV_L, and V_1 to V_6; marked elevation of the RS-T segment in Leads II, III, and aV_F, there being almost monophasic action curves in the latter two leads. The Q wave was absent in Lead II and rather small in Leads III and aV_F. In spite of the absence of deep Q waves at these points, the tracings were regarded as evidence of acute posterior myocardial infarction.

Shortly after admission to the hospital the patient went into shock, and expired twelve hours following admission.

At postmortem examination the heart weighed 400 grams. The coronary arteries were found to be quite sclerotic and tortuous and showed many areas of markedly reduced caliber, most obvious in the branches of the left coronary artery. A fresh thrombus completely occluded the left anterior descending coronary artery 2 cm. from its origin. The right posterior descending coronary artery was the site of an old recanalized thrombus 8 cm. from the origin of the artery. The heart (fig. 4, *B*) showed laminated scarring in the posterior wall of the left ventricle 4 cm. in diameter; the scarred area was surrounded by a substantial thickness of ventricular wall. Located subendocardially there was a well-demarcated circumferential rim of purple, soft myocardium occupying one-third of the thickness of the ventricular wall. The papillary muscles of the left ventricle showed similar changes. The subendocardial rim involved the left half of the interventricular septum while the right half remained normal. The upper portion of the muscular septum in the region of the fibrous septum showed no evidence of infarction. Microscopy confirmed the macroscopic impression of a healed posterior myocardial infarction and a recent subendocardial infarction (of eighteen hours' duration) (fig. 4, *C*).

Except for the absence of deep Q waves in Leads II, III, and aV_F, this patient showed the typical changes of posterior myocardial infarction. It is felt that most tracings of this type would be associated with acute posterior infarction but the possibility of subendocardial infarction must be considered. It is also felt that the scarring noted in the posterior wall was electrically silent and that the pronounced electrocardiographic changes noted were all due to the acute insult. This is the only case in this series in which subendocardial infarction resulted from acute thrombotic occlusion of one of the major coronary trunks. In view of the old occlusion of the right posterior descending branch, it seems possible that the left coronary artery carried the main or preponderant blood

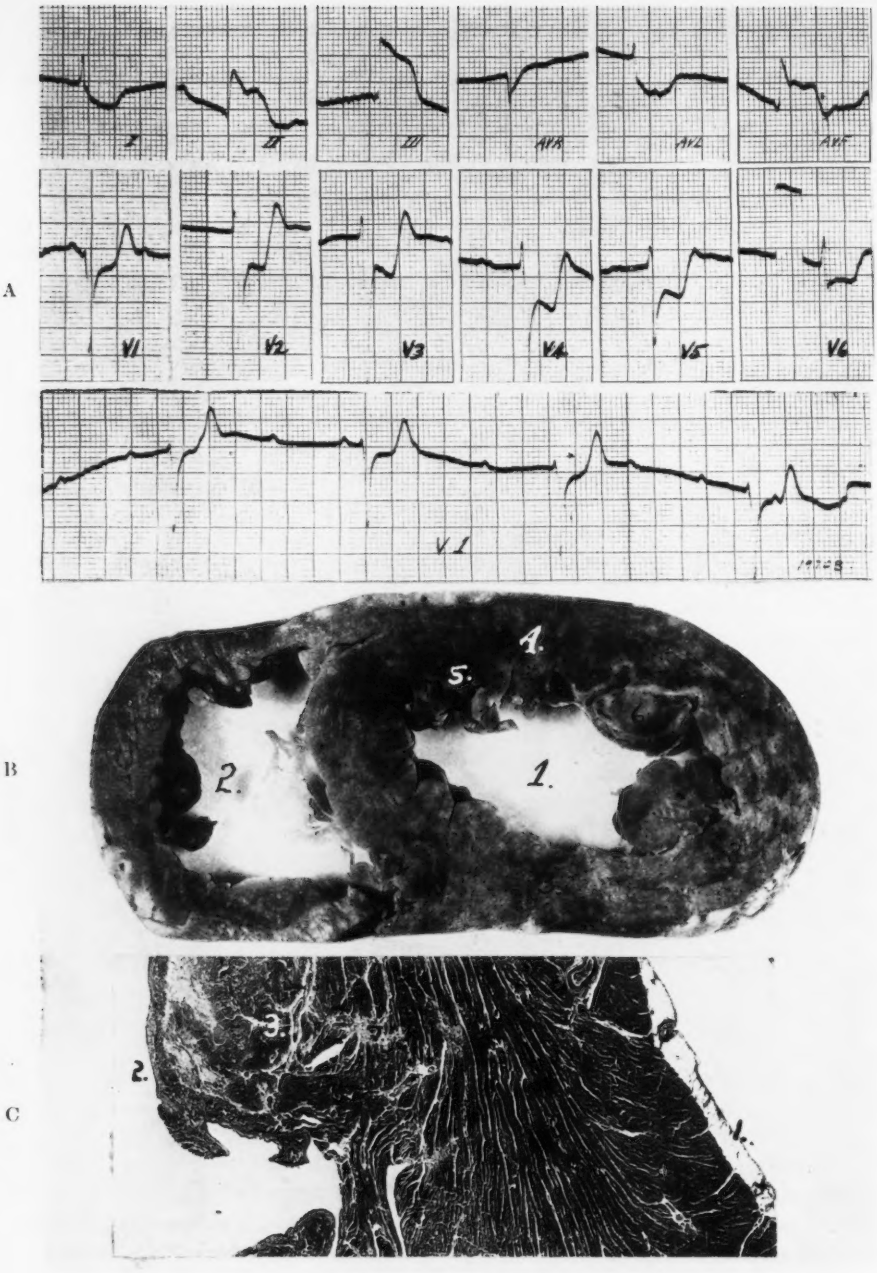

FIG. 4.—Case 4

A, Tracings show depressed RS–T segment in Lead I and elevated RS–T segments in Leads II and III, with monophasic action curve; depressed RS–T segments in the precordial leads and in Lead aV_L with elevated RS–T segment in aV_F. In spite of the absence of a prominent Q wave in aV_F, the diagnosis was acute posterior infarction. *B*, Transverse section of the heart near the atrioventricular sulcus showing old posterior infarct and recent subendocardial infarct most pronounced posteriorly. There was an old recanalized thrombus in the right posterior descending coronary artery and a fresh thrombotic occlusion of the left anterior descending coronary artery. (*1*, Left ventricle; *2*, right ventricle; *3*, anterior; *4*, posterior; *5*, infarcted zone; *6*, infarcted posterior papillary muscle.) *C*, Low-power photomicrograph showing scattered foci of fibrosis and subendocardial zone of acute infarction. (*1*, Epicardium; *2*, endocardium; *3*, zone of infarction.)

supply to the myocardium. Therefore, at the time of fresh occlusion of the left anterior descending coronary artery, the situation was tantamount to global impairment of the blood supply of the heart. However, this must remain a theoretic possibility only, for we have not the precise information regarding the coronary blood supply that would be provided by use of the technic of Schlesinger and Blumgart.[11]

Case 5. (P.B.B.H., 8A469). J.P., a 70 year old white man with hypertension and angina pectoris, was admitted to the hospital on June 28, 1948, because of an attack of acute myocardial infarction. On admission he was in shock with a blood pressure of 82 61. The electrocardiogram (fig. 5, *A*) showed an abnormal form of the ventricular complex with depression of the RS-T segments in Leads I and II, elevation of the RS-T segment in Lead III, and a biphasic T wave in Lead I with late inversion of the T waves in Leads II and III. The unipolar limb leads showed elevation of the RS-T segment in Lead aV_R, depression of the RS-T segment in aV_L and upward bowing with late inversion of the T wave in aV_F; there was no significant Q wave in aV_L or aV_F. The unipolar chest leads showed marked elevation of the RS-T segments in V_1 to V_4, tall R waves, depressed RS-T segments, and inverted T waves in V_5 and V_6. These changes were interpreted as characteristic of left ventricular hypertrophy and in addition as showing changes very suspicious of myocardial infarction of uncertain location, possibly transseptal (Roesler-Dressler) or subendocardial. The patient expired sixteen hours after the onset of the attack.

Autopsy showed cardiac enlargement (the heart weighed 600 grams) and coronary artery sclerosis without occlusion. Section of the heart (fig. 5, *B*) revealed a circumferential pale zone of myocardium 0.4 cm. in thickness beneath the endocardium studded with minute soft foci dark red and black in color. This zone became transmural at no point. Microscopic examination (fig. 5, *C*) showed this circumferential zone to be freshly infarcted (approximately sixteen hours' duration). When the gross sections of the heart were fixed it was noted that the borders of the infarct were serrated rather than linear; this was confirmed microscopically.

In reviewing the electrocardiograms in this case it might be conjectured that the standard and unipolar extremity leads showed a composite effect of posteroseptal or subendocardial infarction and left ventricular hypertrophy. Thus, whereas the RS–T segments in Leads I and aV_L were depressed, the T wave in these leads was biphasic (minus-plus) rather than inverted, and the T wave in Lead III was biphasic (plus-minus) rather than upright. However, since tracing of this sort may be seen in uncomplicated left ventricular hypertrophy, a definite statement in this regard is not warranted.

Case 6. (P.B.B.H., 7A55). H.G., a 65 year old business man, with angina pectoris and hypertension, was admitted to the hospital on October 26, 1947, for excision of carcinoma of the rectum. The electrocardiogram (fig. 6, *A*) made one day after admission showed an abnormal form of the ventricular complex with depression of the RS-T segments in Leads I and II, biphasic T waves in Leads I and II, and deep QS waves in Lead III. The axis deviation index was plus 21 indicating an abnormal left-axis deviation. The unipolar limb leads showed a small Q wave, an embryonic R wave, a small S wave, and an R′ approximately equal to S in Lead aV_F but the total voltage was small in this lead. Unipolar chest leads showed elevation of the RS-T segments in Leads V_1 to V_4 and depressed RS-T segments with biphasic T waves in Leads V_5 and V_6. These tracings were interpreted as characteristic of left ventricular hypertrophy.

Surgery was carried out on the seventh hospital day. During the procedure the blood pressure dropped despite various therapeutic measures, and never returned to its preoperative level, and the urinary output was low. On the second postoperative day, the patient complained of distress in the epigastrium and a pericardial friction rub was heard. Profound changes now appeared in the electrocardiogram (fig. 6, *B*). There was a depression of the RS-T segments in Leads I, II, and III, maximal in Lead II. The RS-T segment in Lead aV_F was depressed but a Q wave was present in neither aV_L or aV_F. The unipolar chest leads showed a late intrinsicoid deflection (R′) in V_1 and V_2; a depressed RS-T segment in V_1 to V_6; maximal in V_3 to V_5; biphasic T waves in V_2 to V_4, and inverted T waves in V_5 and V_6. This tracing was regarded as very suggestive of subendocardial infarction of the anterior wall of the left ventricle.

The patient continued to do poorly. On the following day an electrocardiogram was made but owing to technical difficulties only Leads I and II were recorded. However, as incomplete as the study was, there was adequate electrocardiographic evidence to suggest posterior transmural infarction, for Lead II now showed a small Q wave and elevated RS-T segment (fig. 6, *C*). Later that day the patient went into profound shock, had a convulsion, and died.

The postmortem examination showed the heart to be enlarged, weighing 610 grams, with a left ventricular thickness of 2.5 centimeters. The infarction involved the subendocardial aspect of the

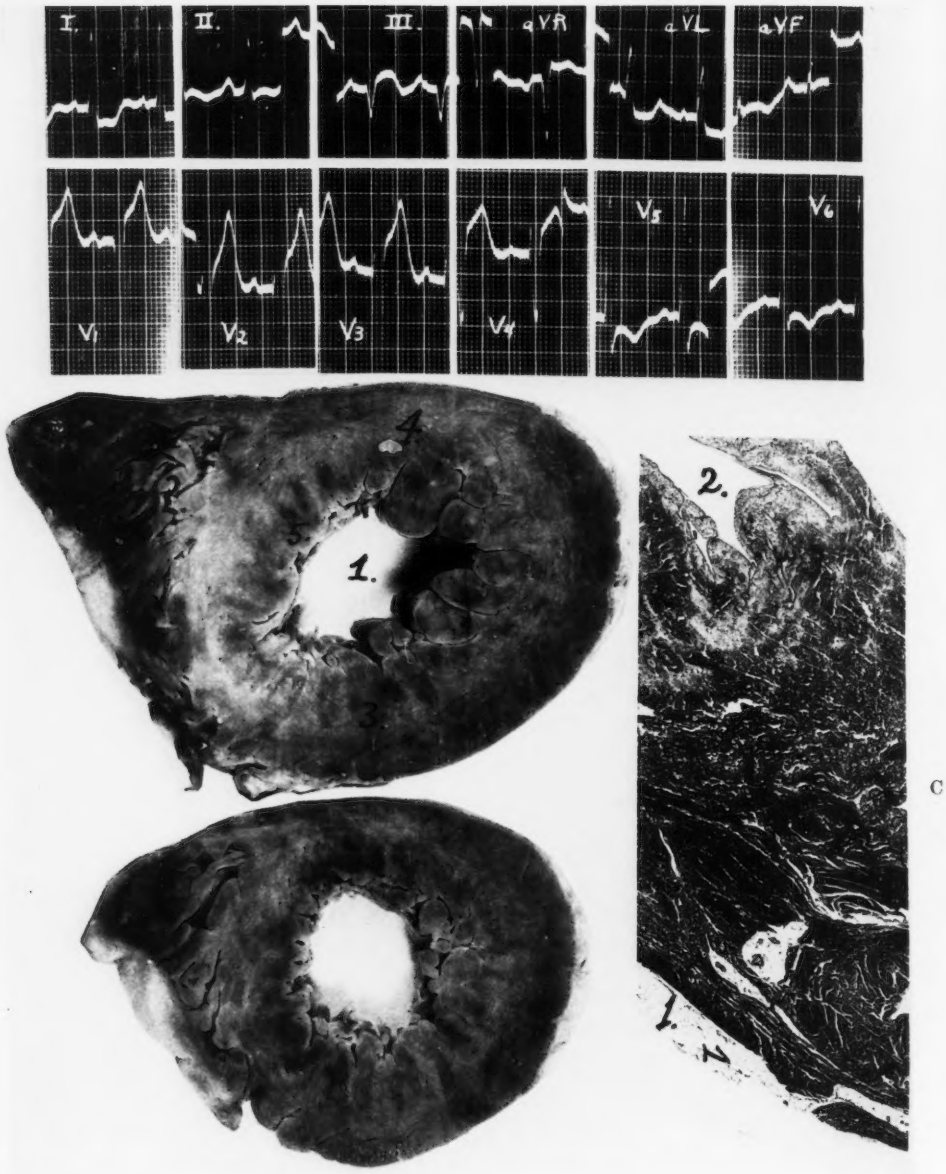

FIG. 5.—Subendocardial Infarction and Left Ventricular Hypertrophy (Case 5).

A, Tracings show depression of RS–T segments and biphasic T wave in Lead I; elevated RS–T segment in Lead III; elevated RS–T segment in aV_R; depressed RS–T segment in aV_L; elevated RS–T segment in V_1 to V_4; tall R waves in unipolar chest leads; depressed RS–T segments and inverted T waves in V_5 and V_6; no prominent Q wave in Lead III or Lead aV_F. Tracings are characteristic of left ventricular hypertrophy and seem suspicious of superimposed myocardial infarction. *B*, Transverse sections through upper and lower halves of the heart showing thick left ventricle and circumferential purple subendocardial zone of infarction with serrated margins. (*1*, Left ventricle; *2*, right ventricle; *3*, anterior; *4*, posterior; *5*, infarcted zone.) *C*, Low-power photomicrograph showing intermingling of fibrotic (pale) and infarcted (dark) foci beneath the endocardium. (*1*, Epicardium; *2*, endocardium; *3*, infarcted zone.)

anterior, lateral, and septal (left side) portions of the left ventricle and was transmural in the posterior wall of the left ventricle. Microscopic examination showed a recent myocardial infarction. There was also a fibrous scar on the anterior wall of the right ventricle near the interventricular septum measuring 1.5 by 3.5 cm.; some scarring was also evident in the middle portion of the interventricular septum. The coronary arteries showed severe arteriosclerosis but no total occlusion, thrombosis, or subintimal hemorrhage.

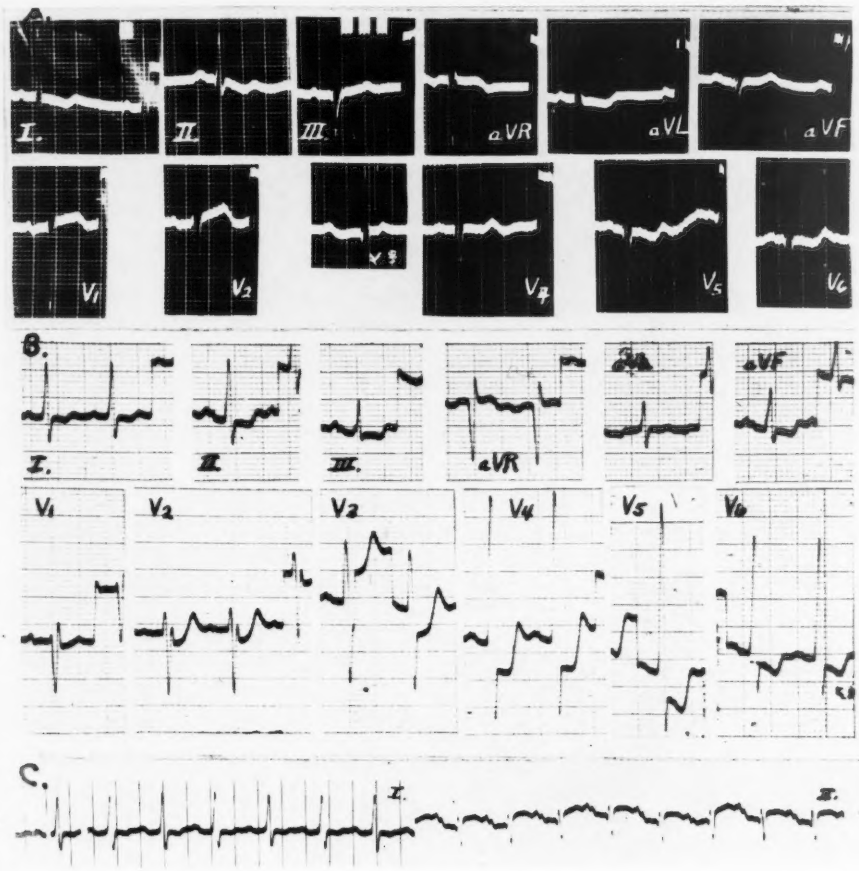

FIG. 6—Acute Subendocardial Infarction as a Prelude to Transmural Posterior Infarction (Case 6).

A, Preoperative tracing is characteristic of left ventricular hypertrophy and shows notched QRS wave in aV_F predominantly below the isoelectric line.

B, Tracing made the second day following operation. The hypotension persisted postoperatively. There is now depression of the RS–T segments in Leads II, III, and aV_F; elevation of the RS–T segment in Lead aV_R with late inversion of the T wave; striking depression of RS–T segments in V_2 through V_6; no Q wave in Lead III or aV_F. These tracings were regarded as very suggestive of subendocardial infarction with incomplete right bundle branch block.

C, Leads I and II only, made on the third postoperative day. There are now a small Q wave and elevated RS–T segment in Lead II which were considered as evidence of acute posterior myocardial infarction. Postmortem examination showed a fresh infarct which was subendocardial on the lateral, anterior and septal aspects of the left ventricle, transmural on its posterior aspect.

This case is of interest because, like some described by Pardee and Goldenberg[4] and by Alzamora,[6] the infarction apparently began as a subendocardial process, then became trans-

mural, and also in that the occasion under which it developed was postoperative hypotension.

Discussion

In an electrocardiographic-pathologic correlation of this sort it is important to bear certain facts in mind. First, the physicochemical phenomenon need not have reached the stage of an anatomic lesion before its electrical effects have become apparent. The functional disturbances which produced the electrocardiographic phenomena may thus have been much more extensive than the structural changes seen at autopsy. Therefore, one would not expect the distribution of the latter to correspond exactly with that of the former. Secondly, by choosing those cases (all but the last—Case 8, to follow) with a fatal issue, it is possible that a more serious prognosis has been attributed to the electrocardiographic changes observed than they necessarily warrant. Finally, in the natural electrocardiographic sequence of transmural infarction, displacement of the RS–T segment may precede the inception of QRS changes. Often the latter do not develop until the former have regressed. Experience has shown that a diagnosis of myocardial infarction is not warranted on purely electrocardiographic grounds unless both QRS and RS–T changes are recorded. In the presence of adequate supporting clinical evidence the diagnosis may be made on the basis of changes in the RS–T segment alone. The failure of QRS changes to appear early in the course of a clinical episode may then be due to the fact that infarction is not present, that infarction is limited to the subendocardium, or that evidence of transmural infarction has not yet developed but will with the passage of time. Indeed, the patient may die before these changes have become apparent. However, the persistent absence of QRS changes over a prolonged period in the face of RS–T displacement and corroborative clinical evidence of infarction would be more suggestive of a process limited to the subendocardium. The most striking feature of the tracings recorded in the present series, therefore, is the absence of characteristic signs of infarction. With the possible exception of figure 6,*C* (taken from the only individual who developed transmural infarction) none of the records would justify the diagnosis of infarction on the basis of the electrocardiographic changes alone. But in each case the electrocardiographic findings in conjunction with the clinical picture might justify the suspicion of subendocardial infarction.

A fair number of reports of cases with myocardial damage limited to or predominating in the subendocardial layers of the heart have already appeared in the literature. Bayley's[12] case showed myocardial necrosis more extensive at the subendocardial surfaces and apex than at the epicardial surfaces of the ventricular muscle. The electrocardiograms in this case showed the so-called "injury against the rule," that is, displacement of the RS–T segments which are the reverse of those which occur in acute pericarditis. The first of 2 cases of myocardial infarction reported by Langendorf and Kovitz[2] showed predominantly, and the second apparently exclusively, subendocardial involvement. Rather atypical bipolar (Leads I to III and CF_2, CF_4, and CF_5) electrocardiograms were recorded in these cases but RS–T depression over the left precordium was not described. The case of Price and Janes[3] with tracings (Leads I to III and IVR) ascribable to posterior or posterolateral myocardial infarction, showed extensive subendocardial infarction. This was the first case in which the correspondence of the myocardial damage to a specific muscle bundle was suggested. The muscle corresponding to the subendocardial fibers of the superficial bulbospiral muscle was involved in this case.

Wilson and his co-workers[13] showed that in myocardial infarction in man, as well as in experimental infarction in dogs, the endocardial aspect of the infarct is almost always larger than the subepicardial aspect. In many of their canine experiments the infarct did not penetrate the ventricular wall or was transmural over only a small area. When the infarct was transmural, deep QS waves were recorded. Where the infarct was subendocardial, as at the margins of a transmural infarct, there were abnormally large Q waves followed by subnormal R waves in the direct leads. There is no reason, therefore, why subendocardial infarcts

should fail to produce QRS changes. Since none were found in any case in the present series it would seem that these cases do not represent subendocardial infarction in general, but subendocardial infarction of a special kind.

Wilson and his associates have also demonstrated that an electrode overlying the epicardial surface of a fresh transmural infarct records an upward displacement of the RS–T segment at the same time that an electrode overlying the ventricular wall opposite this lesion records a downward displacement. Several other physiologic investigations[14–18] have been concerned with the electrical effects of injury of the endocardium or subendocardial layers of the myocardium, particularly as concerns displacement of the RS–T segments. The gist of these studies is that injury confined to the subendocardial layers produces RS–T elevation in leads from the adjacent ventricular cavity as well as in leads from the epicardial aspect of the opposite ventricular wall, while RS–T depression is noted when the exploring electrode is over the epicardial aspect of the affected ventricular wall.

These studies point out the desirability, in evaluating the question of subendocardial infarction, of determining cavity as well as surface potentials. Cavity electrograms obtained by catheterization of the cardiac chambers in the experimental animal can give this information, but this is out of the question with human subjects suspected of myocardial infarction. It is here that unipolar extremity electrocardiography is most helpful. By virtue of the relatively fixed position of the base of the heart, the ring of the auriculoventricular valve faces the right shoulder. As a result, cavity potentials are transmitted through this ring to the right shoulder and the study of right-shoulder potentials (V_R or aV_R) gives virtually the same information as does a catheter electrode within the ventricular chamber. If the heart is in the vertical position electrically, the left shoulder (V_L or aV_L) may also reflect cavity potentials. A slight degree of elevation of the RS–T segment in Lead aV_R may be within normal limits. In 4 of the 6 cases of subendocardial infarction here recorded, however, aV_R showed a rather pronounced degree of upward displacement of the RS–T segment consistent with orientation of the injured area toward the ventricular cavity.

Pruitt and Valencia[17] commented on the difficulty of producing subendocardial damage of sufficient extent and severity to produce measurable electrical effects while still sparing a zone of uninjured myocardium between the traumatized tissue and the epicardium. Nature, it seems, can fulfill the conditions of this experiment much more readily than can the physiologist. This has been explained as the result of the fact that the heart consists not of an homogenous mass of muscle but of an intricate system of interlacing muscle bundles with a spiraling, whorled arrangement. The disposition of these muscle bundles has been described by Mall,[19] Robb,[20] and Lowe and Wartman.[21] Without describing in detail the origin, insertion, and course of these muscle bundles, and neglecting the muscle bundles which make up the right ventricle, it may be stated that the superficial sinospiral muscle constitutes roughly the subendocardial few millimeters as well as the subepicardial few millimeters of the anterior half or so of the left ventricle, while the superficial bulbospiral muscle has a roughly similar distribution posteriorly. Both of these, the superficial sino- and bulbospiral bundles, make up the entire thickness of the apical one-fourth of the left ventricle. The greater bulk of the muscle mass of the basalar three-fourths of the left ventricle lying between the subendocardial and subepicardial distribution of these superficial muscles is made up of three muscles —the deep bulbospiral, deep sinospiral, and the scroll muscle. These bundles have each their own blood supply.[21] Lowe has demonstrated how injury can selectively involve specific muscle bundles.[22] He felt that the cylindric scars sometimes seen in the ventricular walls may be due to obstruction of one of these small coronary branches. However, no reported case of subendocardial infarction in the small arteries was described nor were thrombi found in any of the smaller vessels in this series. Furthermore, since the parent artery gives branches to both the subendocardial and subepicardial portions of the superficial muscles, one would expect to find descriptions of simultaneous

infarction or scarring of the subepicardial and subendocardial shells. It seems, therefore, that some factor other than vessel obstruction is generally responsible for the necrosis of the subendocardial muscle bundles. Recent publications have tended to stress another aspect of the blood supply to the deeper muscle bundles. It has been pointed out, for example, that the blood supply to the left ventricle is derived from main coronary arteries which course down the epicardial aspect of the ventricles, giving rise to perforating branches at right angles to the main artery, and that these reach well into the subendocardium where there are apparently diffuse anastomotic channels.[23] A gradient of pressure existing at the height of systole between the more superficial and deep layers of the ventricular wall has been demonstrated.[24] Except for possible nourishment directly from the left ventricular chamber or via the thebesian channels, or through collateral subendocardial anastomoses, the subendocardium, being that part of the myocardium farthest removed from its blood supply, is the most vulnerable to partial or complete deprivation of its blood supply. It would, therefore, be in these remote parts of the heart that global (shock, anemia, syphilitic ostial disease, and like affections) rather than zonal restriction of coronary flow might be manifest.

The common denominator in all of our cases and in the few described in the literature was found to be a deficient irrigation, not of a single coronary artery, but of the entire coronary system, be it due to clamping down on coronary flow at its source by syphilitic ostial disease, to shock however produced, or to any condition producing systemic hypotension and consequent diminution of coronary blood flow. The occurrence of single or multiple coronary occlusions has been described under such circumstances by Blumgart, Schlesinger, and Zoll[25] but in their cases a subendocardial distribution was not noted. The cases described above, then, are of the kind in which all, or almost all, of the subendocardial muscle becomes ischemic or infarcted as a result of a general disturbance of the systemic (shock) or of the coronary circulation. Under these circumstances it would seem that the forces produced in one part of the ventricular muscle may be cancelled by the effects produced in another. A uniform ischemia of all the subendocardial muscle would be expected to produce downward RS–T displacement in all of the usual leads except aV_R, but it could hardly produce Q waves even after RS-T displacement had disappeared, for there would be nothing to make the ventricular cavities negative. As a matter of fact, if all of the subendocardial muscle failed to respond, the ventricle could not be activated. It must be supposed that the affected muscle did respond but responded subnormally (with a reduced change in the voltage across the membrane) or that the involvement of the subendocardial muscle was extensive but spotty.

This concept of coronary insufficiency was first developed by Büchner.[10] He was well aware of the RS-T depressions developing in the precordial leads in some of the cases and of the subendocardial distribution of the resulting ischemia or infarction. This aspect of the concept was elaborated by Master[9, 26] and the role of the collateral circulation by Blumgart and his colleagues.[11]

It is possible that study of the muscle bundle distribution may explain a rather curious finding in the pediatric literature. This is the so-called thickened endocardium which has been reported with or without hypertrophy of the heart in children, and has been attributed in some cases to a previous endocarditis. Some of the cases, however, lacked any evidence of inflammatory reaction. In light of the more recent anatomic studies, it is suggested that the apparent thickening of the endocardium may actually be due to fibrosis of the superficial sino- or bulbospiral muscles. In one such case[27] the left anterior descending coronary artery was narrowed and among other possibilities it was suggested that the change may conceivably have been due to the consequent coronary insufficiency. Future studies of this condition should include a careful examination of the blood supply to the heart.

Alzamora[6] felt that subendocardial infarction was a relatively benign process and that perhaps in only a very few subjects is the condition found at necropsy. That this is not necessarily true is suggested by the present study

in which in 6 of 65 cases of fatal myocardial infarction a subendocardial distribution of the process was shown. It is our impression that these cases represent a type of myocardial infarction of particular distribution and arising under particular circumstances, but nonetheless with similar pathologic physiology and the same uncertain prognosis of the entire group of myocardial infarction. It seems to us that to designate these merely as cases of coronary insufficiency is to minimize their gravity.

Under certain circumstances the described electrocardiographic changes need not indicate subendocardial infarction. Their occurrence as a transient phenomenon following or during spontaneous or induced angina pectoris has been well established and is the criterion upon which are based certain functional tests for that condition. Their inception and reversibility during other disturbances is also quite familiar. The electrocardiographic tracings shown in figure 7,*A* are those of a 64 year old woman with hypertensive heart disease and angina pectoris who developed auricular fibrillation during a stormy postoperative course following cholecystectomy. The ventricular rate during the attack of abnormal rhythm was 164. At this time pronounced RS-T depression was noted in Leads I, II, aV_F, and V_3 to V_6 and RS-T elevation in Lead aV_R—changes of the same order as those described above. On reversion to normal rhythm (Fig. 7,*B*) following quinidine therapy the rate slowed to 56 and the RS-T segment displacements returned to the isoelec-

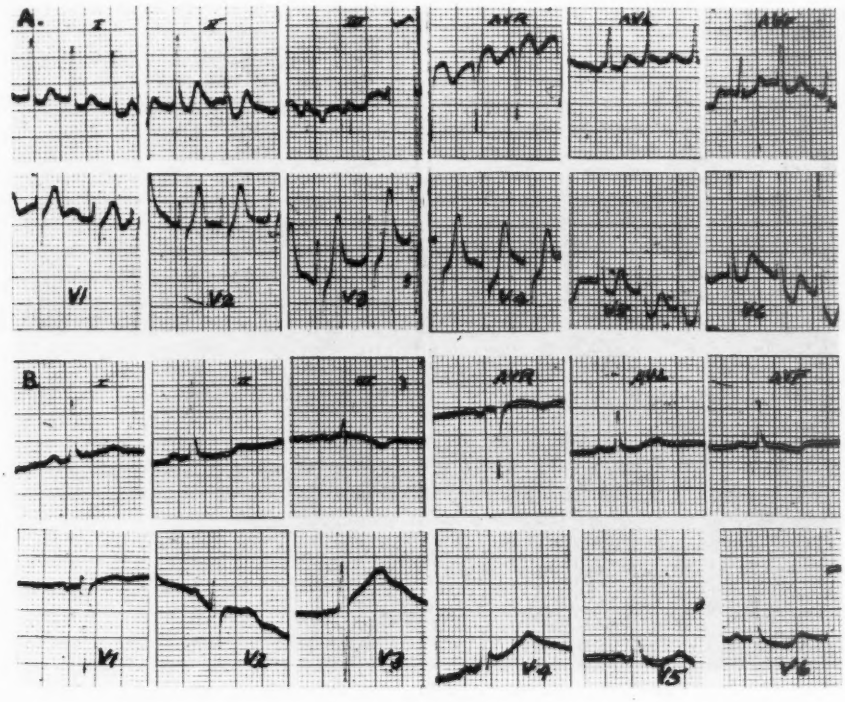

FIG. 7.—Case 7

A, Tracings made during a paroxysm of auricular fibrillation showing depressed RS-T segments in V_3 through V_5 and to lesser extent in V_1, V_2, and V_6; slight elevation of RS-T segment in aV_R.

B, Curves showing reversion to normal rhythm brought about by quinidine therapy. Note disappearance of RS-T deviations. The first set of tracings resemble those occurring with subendocardial infarction, but the changes were reversible and possibly attributable to ischemia. Autopsy showed coronary sclerosis but no infarction.

tric level. This patient's death was due to surgical complications. At autopsy some coronary sclerosis was noted but no subendocardial infarction. Electrocardiographic tracings shown in figure 8,*A* were obtained from a 59 year old housewife during a paroxysm of auricular tachycardia which had lasted about twenty-four hours. The RS-T displacements here noted are quite commonly seen during such attacks, especially those of considerable duration. These changes are quite the opposite of those recorded in simple physiologic tachycardias where the rapid rate is apt rather to produce an elevation of the RS-T segment.[28] Figure 8,*B* represents tracings made of the same patient immediately following reversion to normal rhythm with right ocular pressure. The prompt return of the RS-T segment to the isoelectric line is quite striking. Generally, as in the examples cited, the reason for the changes will be quite obvious, be it angina pectoris or paroxysmal rapid heart action. Their development and persistence during an episode suggestive of acute myocardial infarction would be much more suggestive of actual infarction in the subendocardium.

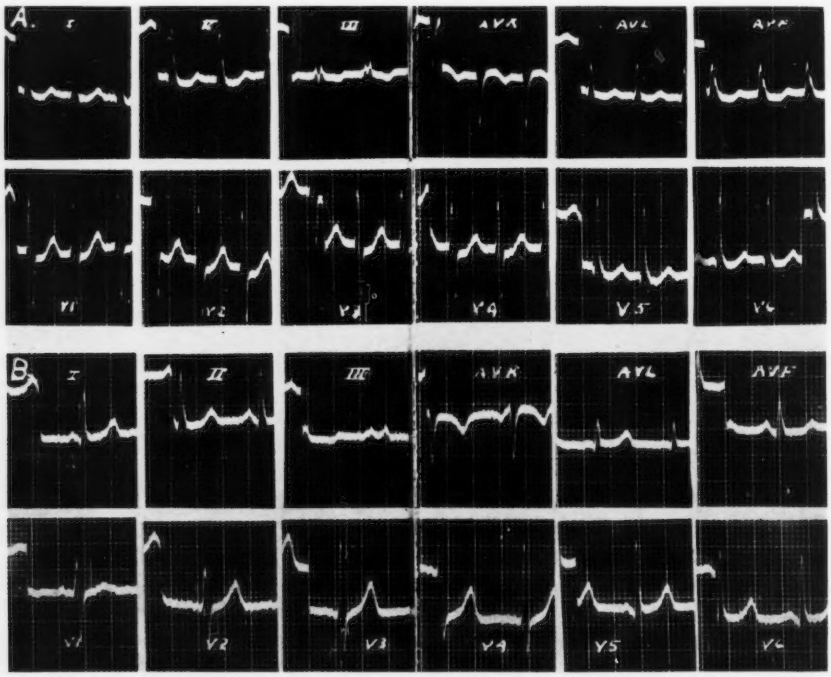

FIG. 8.—Case 8

A, Tracings made during paroxysm of auricular tachycardia showing RS–T depression in V_1 through V_6; most pronounced in V_2 through V_4; slight elevation of RS–T segment in aV_R.

B, Tracings made immediately following restitution of normal rhythm showing return of RS–T deviations to the isoelectric line. Because of their reversibility, the changes recorded in *A* may be attributable to subendocardial ischemia rather than infarction.

It is possible that the frequency of this finding in the present series may result, in large part, from our interest in the condition. We feel that if the electrocardiographer is alert to the type of tracing inscribed in this condition he will detect or suspect more cases of myocardial infarction limited to or predominant in the subendocardial layers of the myocardium, and that he will find many cases in which the process begins as a subendocardial

one and subsequently develops the characteristic electrocardiographic stigmas of transmural infarction. Meticulous pathologic examination may confirm this subendocardial distribution in a larger proportion of cases than hitherto reported.

Summary

Six instances of subendocardial myocardial infarction were encountered at autopsy among 65 cases of myocardial infarction. In 3 instances, the diagnosis was made or strongly suspected on electrocardiographic grounds. In a fourth case this possibility was entertained but acute cor pulmonale was considered more likely. In the fifth case the electrocardiogram was characteristic of left ventricular hypertrophy and in the last, suggestive of acute posterior myocardial infarction. The electrocardiographic clue to this condition was depression of the RS-T segment over the precordium, elevation of the RS-T segment in Lead aV_R and the absence of a prominent Q wave in aV_F, findings which, of themselves, do not justify the diagnosis of infarction, but which in conjunction with the clinical picture may herald transmural infarction or suggest subendocardial infarction.

In three instances there was extensive coronary arteriosclerosis without occlusion. In one, the left anterior descending coronary artery was occluded by a fresh thrombus but in view of a previous old occlusion of the right posterior descending coronary artery, the former vessel probably carried the greater part, if not all, of the blood to the left ventricle. In the second (Case 5), the arteriosclerosis was associated with syphilitic narrowing of the coronary ostia. In the third (Case 6), it followed postoperative shock. This last case was the only one in this series in which the subendocardial infarction was the prelude to a transmural infarction. In all of the cases, the infarction was limited to a rim of myocardium, usually circumferential, and distributed subendocardially with a tendency to involve the papillary muscles. Thrombi were not seen in the smaller coronary vessels in the neighborhood of infarction. The remarkable clinical feature of this group of cases was the uniform presence of shock. The facts presented here are consistent with the concept that the electrocardiographic and pathologic features of subendocardial infarction develop characteristically in conditions associated with impairment of the total coronary blood supply.

Addendum

We have reviewed the comprehensive and thorough studies of Gordon Myers and his colleagues since the present paper was submitted for publication. These observers found numerous instances of subendocardial infarction either localized to certain segments of the left ventricle (antero-septal,[29] antero-lateral,[30] lateral,[31] septal,[32] etc.) or, like those reported here, circumferential and involving all or most of the subendocardium; these were found in various stages of development from acute through organizing to healed. Old scars which were purely subendocardial or which were subendocardial extensions of transmural infarcts were generally correlated with QR deflections but, curiously, at times with QS deflections. In some cases QR complexes in Lead aV_F (Goldberger) were noted in association with posterior subendocardial infarction. Acute or subacute subendocardial infarcts might be associated with depressed, isoelectric or elevated RS-T segments. Case 14 of their study[29] showed pathologic changes such as those described in the present paper and, though the RS-T segment in Leads I and II was depressed, the electrocardiographic sequence consisted of the appearance and subsidence of changes of acute antero-septal infarction. Case 38[30] resembles the acute subendocardial infarcts described here in all respects. In case 146,[31] although the electrocardiographic tracings resemble those described here, postmortem examination showed a transmural lateral infarct with anterior subendocardial "ischemia" only. These workers gave a number of explanations for the puzzling failure of Q waves to develop in acute subendocardial infarction. It seems to us that this is linked up with the extent of the subendocardial infarct. As a result of the extensive infarction of the entire subendocardial rim, no important area of the wall opposite the recording electrode is able to get a "head start" in being activated; hence a Q wave does not

develop at the recording electrode. Electrically inconspicuous but adequate islands of intact myocardium are interspersed with the infarcted areas and transmit the activating impulse to the relatively healthy subepicardial layers. Yet the injured area is formidable enough to present a large "current of injury" oriented toward the endocardial aspect of the ventricle; therefore, RS-T segment depressions develop over the left ventricle and RS-T elevation at lead aV_R.

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Membrane Resting and Action Potentials of Single Cardiac Muscle Fibers

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An initial report is made on the electrocardiogram of a single heart muscle cell in vivo. The potential variations obtained by electrodes placed on opposite sides of the membrane of a heart muscle fibre are 50 to 100 times as large as those recorded by standard limb leads. The observations support the assumption that during activation the cell interior becomes positive with respect to its surrounding (depolarization, followed by polarization reversal). Induced alterations in shape and form of the action current of a single heart muscle fiber should provide further insight into the nature of the normal and abnormal electrocardiogram.

THE development of the glass capillary microelectrode by Graham and Gerard[2] and its subsequent improvement by Ling[5] and by Hodgkin and Nastuk[4] has made available a technic which permits the direct observation of the electrical events of single cells in multicellular tissues. It occurred to us that the recording of potential variations of individual heart muscle fibers would be of particular interest because information thus obtained would contribute to the understanding of basic problems of electrophysiology and the interpretation of the electrocardiogram. Using the following technic, we have recorded what we believe to be membrane resting and action potentials from single heart muscle fibers.

Leopard frogs were pithed and skinned; the heart was exposed, and filled and coated with melted 10 per cent Gelatin-Ringer's solution at 26 C. The preparation was cooled to solidify the gelatin. This immobilized the heart so that only slight motion was visible under a magnification of 12×. Electrical and essentially isometric mechanical systole still occurred. After immobilization the entire preparation was covered with frog Ringer's solution. The heart continued to beat for several hours so that no external stimulus was needed. Glass capillary microelectrodes made by the method of Graham and Gerard[2] as refined by Ling[5] and by Hodgkin and Nastuk[4] were inserted into single ventricular muscle fibers by the use of a micromanipulator. The outer diameter of the electrode at the tip ranged from 0.5 to 2.0 micra.

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The indifferent electrode was placed at convenience in the bathing medium. In later experiments, a 20 micra capillary electrode was placed on the surface within 0.5 mm. of the intracellular electrode. It served either as a return electrode or as an exploring contact for simultaneously recorded surface electrocardiograms. The electrodes were connected through calomel half-cells and a high input resistance DC amplifier to a millivoltmeter and a Cambridge film recording string galvanometer.

On the basis of experience gained in a series of preliminary experiments, the tip of the microelectrode was assumed to lie in the interior of a relatively undamaged fiber when the record obtained showed the following characteristics: (1) a series of monophasic action potentials showing (2) overshoot and (3) no appreciable change of shape or form during the series; (4) a resting potential of more than 50 millivolts; and (5) a disappearance of the monophasic action potential and the reappearance of the surface electrocardiogram on withdrawal of the electrode.

Resting potential. The average membrane resting potential in 175 measurements on 15 preparations taken at temperatures from 12 to 16 C. was 62.0 millivolts with a range of 50 to 90 millivolts. No corrections were made for junction potentials between the microelectrode and the cell interior. For an electrode filled with 3 molar potassium chloride solution, rough

calculations suggest that correction for this potential would increase the observed values by less than 3 millivolts.

Action potential. Typical membrane action potentials are illustrated in figure 1. It is apparent from the figures that the action potential exceeds the resting potential. This shows a reversal of the membrane polarity during activity. In 215 measurements of 15 preparations taken at 12 to 16 C. the action potential exceeded the resting potential by an average of 30.4 per cent. The mean value of 176 measurements of the action potential was 80.8 millivolts with a range of 65 to 115 millivolts. In 13 out of 276 records, hyperpolarization of the membrane following recovery occurred. The average value was 10 per cent, and the highest observed hyperpolarization was 12.7 millivolts.

The duration of the action potential varied from 0.4 to 1.0 second and increased approximately linearly with cycle length over this range of measurements.

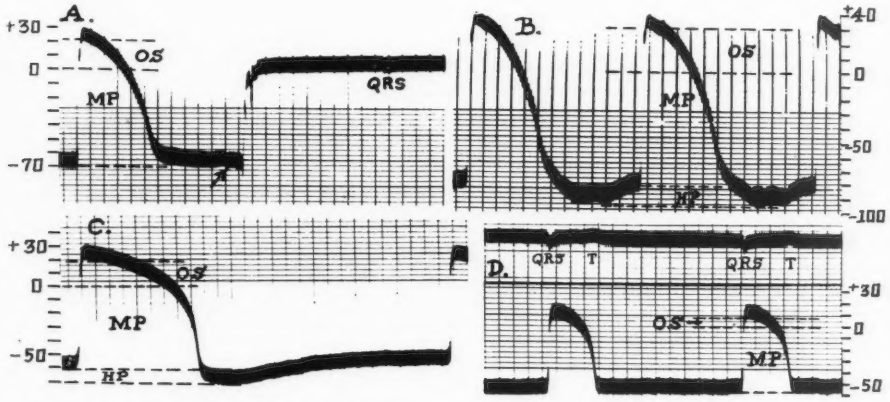

FIG. 1.—Action potentials of single cardiac ventricular fibers. (M.P. Resting membrane potential, O.S. Overshoot, HP Hyperpolarization.) All measurements made from bottom of string shadow. Ordinates—millivolts; abscissae—time. Vertical lines 0.1 second apart.

A. Action potential of single ventricular fiber. Arrow indicates start of withdrawal of electrode from cell to show return of string to zero value and presence of small surface electrocardiogram. (QRS)

B. Action potential showing marked hyperpolarization during recovery.

C. Action potential of longer duration.

D. Action potentials of single fiber (below) and simultaneous surface electrocardiogram (above).

DISCUSSION

As may be seen from figure 1, the electrical sequence of events in a single ventricular fiber of the frog is as follows: During diastole a fairly constant voltage, the resting potential, exists between the inside and outside of the fiber with the inside negative to the outside. The onset of electrical systole is marked by a quick reversal of polarity of the membrane potential (depolarization and overshoot of the action potential). Following this reversal the membrane voltage, slowly at first and then more rapidly, returns to its resting value. In a small percentage of observations the membrane potential becomes greater than its resting value and then returns to normal (hyperpolarization).

In some experiments, surface electrocardiograms were recorded simultaneously with the internal events of single fibers and show the correspondence between the two. Figure 1, *D* shows that the QRS complex coincides with the sudden depolarization of the fiber and the T wave with the end of the repolarization process.

Because of the necessity for immobilization of the heart, no mechanograms have yet been obtained simultaneously with the electrical records of a single fiber. Visual observation, however, showed that contraction of the heart muscle occurred very shortly after the depolari-

zation and that relaxation occurred shortly before or coincident with the end of repolarization.

The demonstration of overshoot of the action potention in heart muscle raises the question as to whether it may not be a general phenomenon in all excitable tissues. Curtis and Cole[1] and Hodgkin and Huxley[3] showed overshoot in the squid giant axon, and Hodgkin and Nastuk[4] reported its occurrence in frog sartorius muscle. The latter authors give values for frog sartorius from which the overshoot can be calculated to be 32 per cent, a figure that compares well with our value of 30.4 per cent for frog heart.

Although the electrocardiogram is multiphasic when taken with indirect or semidirect leads or even on direct recording from the heart, the above results make it clear that the basic electrical event of the heart cell as seen by electrodes on opposite sides of the membrane of a single fiber is a simple monophasic wave. The rapid depolarization of the membrane coincides with the QRS complex as observed on a simultaneous surface record, and the end of repolarization coincides with the T wave (fig. 1, *D*). It may be speculated that the hyperpolarization is related to the U wave, but definitive evidence is lacking on this point.

The development of a satisfactory preparation in which single heart fiber potential can be recorded opens the way to investigations of the operation of the pacemaker and the effect of various physiologic and pharmacologic agents (such as electrolytes, epinephrine, acetylcholine and the cardiac glycosides) upon shape, size and duration of single fiber potentials. Work is being continued along these lines.

Summary

By the use of microelectrodes 0.5–2.0 micra in diameter, membrane resting and action potentials have been obtained from single fibers of the frog heart. Resting potentials averaged 62.0 millivolts and action potentials averaged 80.8 millivolts, giving an average overshoot of 30.4 per cent. The action potential was monophasic, with the beginning and end coincident with the QRS complex and T wave, respectively.

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Studies of Congenital Heart Disease

IV. Uncomplicated Pulmonic Stenosis

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Congenital pulmonic stenosis is indicated by cardiac catheterization by the finding of a higher systolic pressure in the right ventricle than in the pulmonary artery. Eight cases of uncomplicated pulmonic stenosis are studied. The findings on history, physical examination, x-ray and fluoroscopy, and electrocardiogram have been analyzed and the variations in circulatory dynamics encountered in these individuals are described in detail.

IT IS generally considered that congenital pulmonic stenosis unaccompanied by other cardiac defects is rare. Recently, Greene and coworkers[1] have made a complete review of the literature and have collected 68 cases. Their article and the book of Brown[2] contain excellent discussions of this disorder.

Cardiac catheterization[3] has made possible an accurate recognition of pulmonic stenosis by the finding of a higher systolic pressure in the right ventricle than in the pulmonary artery.[4] Pollack, Taylor, Odel, and Burchell[5] have recently published a report of 3 cases recognized by this technic, 4 more were reported by Greene and associates[1], and this paper deals with 8 more cases.

Methods

Each patient remained in the hospital for at least four days. A history, physical examination, routine laboratory tests, electrocardiogram, x-ray examination, and fluoroscopy of the heart were carried out. Heart sound tracings were obtained in all cases. On the third day, venous catheterization was performed and the diagnostic routine described elsewhere[4] was performed.

The circulatory dynamics of 5 of the patients were studied at rest and also under conditions of mild and moderate exercise. Pulmonary "capillary" pressure[6, 7] was recorded with saline and Hamilton manometers[8] at rest and at the end of three minutes of exercise. The catheter was then withdrawn to a point near the bifurcation of the pulmonary artery. A No. 21 needle was introduced into the brachial artery, its lumen being kept patent by a slow infusion of saline. When pulse and respiration were at the previous resting level, expired air was collected in a Douglas bag for three minutes, blood samples for oxygen content were withdrawn under oil from the pulmonary artery and brachial artery at the one and one-half minute mark, and pressures from pulmonary and brachial arteries were recorded with Hamilton manometers immediately thereafter. A three minute period of mild exercise followed, expired air being collected in a Douglas bag between two and one-half and three minutes and blood samples under oil at two and three-quarter minutes. Pressures were recorded immediately thereafter. After pulse and respiratory rates had returned to the resting level, exactly the same procedure was carried out during a period of more severe exercise.

Exercise was performed with the patient recumbent, pedaling a bicycle wheel at the foot of the fluoroscope. The only change in position between the resting and exercise periods was that of raising the feet 6 to 12 inches so as to clear the table during pedaling. With both exercise periods, the speed was regulated by a metronome at 56 revolutions per minute (R.P.M.). During mild exercise, the resistance to the wheel amounted to 2 pounds; during the more severe exercise, to between 7 and 11 pounds, as noted in table 2.

Oxygen content and capacity of blood samples were determined by the method of Van Slyke and Neill.[9] Expired air samples were measured in a Tissot spirometer and analyzed in a Haldane apparatus. Cardiac output was determined by the Fick principle. A general idea of the basality of the individual was obtained by comparing the oxygen consumption by the routine hospital basal metabolism test with that obtained by collecting expired

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air in the laboratory. The point of zero reference for pressures was 10 cm. anterior to the spine with the patient recumbent. Mean pressures were determined by planimetry of Hamilton pressure tracings and by means of a saline manometer. Pulmonary vascular resistance proximal to the capillaries was measured by the following Poisseuille formula:

$$R = \frac{(PA_m - PC_m) \times 1332}{CO \text{ (cc./sec.)}}$$

dyne-second-cm.$^{-5}$ and the resistance to blood flow through the stenotic valve was calculated by the following formula:

$$R = \frac{(RV_{sm} - PA_{sm}) \times 1332}{CO \text{ (cc./sec.)}}$$

dyne-second-cm.$^{-5}$, where PA_m = mean pressure in the pulmonary artery in mm. Hg, PC_m = mean pressure in pulmonary "capillaries," RV_{sm} = mean pressure during systolic ejection phase of right ventricle in mm. Hg, PA_{sm} = mean systolic pressure in pulmonary artery in mm. Hg, and CO = cardiac output in c.c./second.

The mean pressures were obtained by planimetry of the Hamilton tracings. For the right ventricle, the ejection phase begins at that point on the rising curve which is equal to the diastolic pressure in the pulmonary artery, and ends at that point of the descending curve which is equal to the pressure at the dicrotic notch of the pulmonary artery tracing. For the pulmonary artery, systole begins at the first upstroke and ends with the dicrotic notch. The accuracy of the measurements varies considerably depending on the fidelity of the pressure tracings. The limitations of Poisseuille's law as applied to circulatory problems are appreciated but we believe that such calculations of resistance serve a useful function.

Case Reports

Case 1. A. J. (P.B.B.H. #7A778) was a 23 year old automobile mechanic who was found to have a heart murmur at the age of 5. He had always been kept from extreme exertion by his physicians and blueness had been observed by others when he swam for short periods or when he was exposed to cold weather. He had never had any chest pain or symptoms of cardiac failure, rheumatic fever, or subacute bacterial endocarditis. On a moderate degree of exertion he had always noted shortness of breath but had been able to work at his profession without difficulty. On physical examination he was a slight, well-muscled young man with minimal prominence of the left precordium. The blood pressure was 122/68. There was no cyanosis or clubbing. The cardiac rhythm was regular. The apex impulse was 1.0 cm. outside the midclavicular line in the fifth intercostal space. The second sound at the apex was split. The pulmonic second sound and mitral first sound were of normal intensity. In the third left intercostal space there was a Grade 4, rough, medium-pitched, systolic murmur, stopping just before the second sound. There was an accompanying thrill but no diastolic murmur. The systolic murmur was widely transmitted in diminished intensity over the precordium and faintly over the back. The lungs were clear, abdominal examination normal, radial and femoral pulses were strong, veins were not distended, and no edema could be discerned. The Hinton test was negative and urinalysis was normal. The hematocrit was 49 per cent, the hemoglobin 16.5 Gm., the white blood cell count and differential normal, and the routine blood chemistries were normal. X-ray and fluoroscopy revealed a heart of normal size. The pulmonary artery was enlarged and pulsating. The pulmonary vascular markings were within normal limits. The electrocardiogram showed incomplete right bundle branch block.

Case 2. R. L. (P.B.B.H. #6A875) was a 26 year old man in whom a heart murmur had been detected in childhood. He had never had symptoms of rheumatic fever, tuberculosis, or cardiac failure. He had always been fond of sports and was an enthusiastic skier. He had never noticed any decrease in exercise tolerance. Four months before admission, he contracted bacteriologically proven subacute bacterial endocarditis which was treated with penicillin in another city and pronounced cured. Because of difficulty in obtaining jobs with his loud murmur, he came to the Peter Bent Brigham Hospital with the hope of being surgically cured. On physical examination he was a burly, well-developed man without cyanosis or clubbing. The heart was not enlarged, the rhythm was normal, and the first sound at the apex was normal as was the aortic second sound. The pulmonic second sound, however, was loud and forceful. A Grade 4 systolic murmur was heard loudest in the third left intercostal space and was transmitted widely over the precordium and back. It was harsh, medium-pitched, and accompanied by a thrill in the pulmonic area. No diastolic murmur was audible. The lungs were clear, neither the liver nor the spleen were palpable, no edema was present, and peripheral pulses were normal. The blood Hinton test was negative, urinalysis was normal, the hematocrit was 47 per cent, the hemoglobin 16.4 Gm., the white blood count and differential were within normal limits, and routine blood chemistries were not remarkable. X-ray and fluoroscopy of the heart revealed 27 per cent enlargement; both right and left ventricles, and the right auricle appearing larger than normal. The pulmonary artery was definitely enlarged and the pulmonary vascular markings appeared normal. By electrocardiogram, right ventricular hypertrophy was present.

Case 3. J. M. (P.B.B.H. #M-71368) was a 22 year old engineering student. He had had a known heart murmur since infancy but aside from slight dyspnea

on extreme exertion he had never noticed any exertional limitation. He had never been aware of cyanosis except for one questionable episode during infancy. There had never been symptoms to suggest tuberculosis, rheumatic fever, or subacute bacterial endocarditis. Physical examination revealed a well-developed young man without cyanosis or clubbing. The blood pressure was 118/80. The cardiac rhythm was normal. The heart was not enlarged to percussion and the heart sounds were inaudible except at the apex. Elsewhere they were obscured by a Grade 6 systolic murmur, harsh in quality, persisting through systole, and maximal in intensity at the second left intercostal space. Here there was an intense systolic thrill. The lungs were clear to percussion and auscultation and there were no signs of congestive heart failure. Laboratory examinations were negative for abnormality as regards blood Hinton, urinalysis, white blood cell count and differential, and routine chemistries. The hematocrit was 45 per cent and the hemoglobin 16.3 Gm. Roentgen-ray examination revealed enlargement of the right auricle and ventricle, no enlargement of the pulmonary artery which did, however, pulsate abnormally, and normal pulmonary vascular markings. There was right ventricular hypertrophy by electrocardiogram.

Case 4. T. M. (P.B.B.H. #2A265) was a 14 year old schoolboy who was known to have had a murmur since early childhood. His only cardiovascular disability had been shortness of breath on moderate exertion, as, for example, running from home plate to first base. He had never had any ankle edema, orthopnea, or progression in his shortness of breath. After heavy exertion, he believed his finger nails became blue. There was no history of tuberculosis, rheumatic fever, or subacute bacterial endocarditis. On physical examination the vital signs were normal. Blood pressure was 130/65. He was a well-developed boy and large for his age. There was no cyanosis or clubbing. The heart was not enlarged to percussion but seemed prominent in the fourth left intercostal space. The pulmonic second sound was accentuated and louder than the aortic second sound. The first sound at the apex was accentuated. There was a Grade 3 systolic murmur loudest in the third left intercostal space and of diminished intensity elsewhere over the precordium. The murmur extended throughout systole, did not run through the second sound, and was coarse in quality and of medium pitch. There was no thrill or diastolic murmur. The lungs were clear, liver and spleen were not felt, the femoral pulses were present, and no edema was observed. The Hinton test was negative. The urine was normal. The hemoglobin was 15 Gm., the hematocrit 48 per cent, and routine blood chemistries were normal. X-ray and fluoroscopy revealed heart and lungs to be normal except for enlargement of the pulmonary artery. The electrocardiogram showed incomplete right bundle branch block.

Case 5. E. R. (P.B.B.H. # M-70294) was a 19 year old stenographer who had been found to have a heart murmur at the age of 4 during an attack of scarlet fever. She had never been cyanotic and had lived a normal life without any untoward symptoms. There was nothing in the history to suggest rheumatic fever, subacute bacterial endocarditis, or tuberculosis. Physical examination revealed a normally developed girl without cyanosis or clubbing. There was a well marked sinus arrythmia. The heart was not enlarged by percussion. A high-pitched systolic murmur, Grade 3, was heard maximally in the fourth left intercostal space, just to the left of the sternum, and was transmitted to a lesser degree over the precordium. No diastolic murmur was heard. The aortic second sound was louder than the pulmonic, the latter being of about average intensity. The lungs were clear, abdomen negative, and there was no edema. The femoral arteries had good pulsations. The blood Hinton was negative, urinalysis normal, the blood hemoglobin 13.2 Gm., and the hematocrit 41 per cent. Routine blood chemistries were normal. The only fluoroscopic and x-ray abnormality was an apparent right auricular enlargement. The pulmonary artery was of normal size. The electrocardiogram was suggestive of left ventricular hypertrophy with intraventricular block.

Case 6. W. P. (P.B.B.H. #7A854) was an 11 year old boy who was discovered to have a heart murmur at the age of 2. He had never noted any cardiac symptoms except for slightly more dyspnea, perhaps, than his playmates on extreme exertion. He had never had cyanosis, pain, or symptoms of rheumatic fever, subacute bacterial endocarditis, or tuberculosis. He enjoyed all kinds of sports. On physical examination he was a big, husky, pleasant boy. The blood pressure was 110/60, the precordium was symmetrical, and there was no cyanosis or clubbing. The heart was not enlarged to percussion. The pulmonic first sound was accentuated and palpable. The aortic second sound was louder than the pulmonic. There was a Grade 5 medium-pitched systolic murmur maximal at the third left intercostal space, transmitted widely over the precordium and back. There was a pulmonic systolic thrill. No diastolic murmur was heard. The lungs were clear, liver and spleen were not felt, and there was no edema. The urine was normal, hematocrit 45 per cent, hemoglobin 15 Gm., and the Hinton test negative. The right auricle and pulmonary artery appeared enlarged by fluoroscopic and x-ray examination. Pulsations of the pulmonary artery were prominent. There was incomplete right bundle branch block.

Case 7. S. C. (P.B.B.H. #3A124) was a 15 year old girl who was found to have a heart murmur at the age of 7. She developed normally, had no physical restrictions, and was always asymptomatic. There was no history of rheumatic fever or bacterial endocarditis. Cyanosis was denied. On physical examina-

tion she was a plump, pleasant young girl without cyanosis or clubbing. The blood pressure was 124/80. There were no arrhythmias or cardiac enlargement. There was a Grade 3 systolic murmur maximal in the second and third left intercostal spaces. There were no thrills or diastolic murmurs. The pulmonic first sound was split and the second sound was accentuated. There were no signs of cardiac failure. Routine blood chemistries were normal. X-ray and fluoroscopic studies of the heart revealed it to be of normal size but the pulmonary artery was enlarged. The pulmonary vascular markings were within normal limits and the electrocardiogram was normal.

Case 8. W. H. (P.B.B.H. #3A383) was a 13 year old boy who had had a normal birth and whose mother did not recall any virus disease during pregnancy. At the age of 1 year, he was found to have a murmur following an episode of becoming "blue." There was no history of subsequent cyanosis. No history of rheumatic fever, subacute bacterial endocarditis, or tuberculosis was obtained. He grew and developed normally and was able to compete in athletics, being the best wrestler in his class. He was unable to support prolonged exertion, however, because of dyspnea. Physical examination revealed a normally developed boy without cyanosis or clubbing. The blood pressure was 122/76. The precordium was moderately prominent on the left and there was a slight left dorsal scoliosis. The apex impulse was in the fifth intercostal space. The first sound was split along the left sternal border and at the apex. In the pulmonic area, the first sound was loud. The pulmonic second sound was of normal intensity. There was a Grade 2, rough systolic murmur maximal in the second and third left intercostal spaces together with a Grade 2, rather high-pitched, early diastolic murmur in the same area. The lungs were clear, no viscera were felt on abdominal examination, the femoral pulses were strong, and there was no edema. The Hinton test for syphilis was negative, urine normal, hematocrit 45 per cent, and white blood cell count and differential were normal. Routine blood chemistries were within normal limits. X-ray and fluoroscopy of the heart showed it to be of normal size with moderate prominence of the pulmonary artery, pulsations of which were more conspicuous than normal. The vascular markings of the lungs were within normal limits. The electrocardiogram was normal.

TABLE 1.—*Findings by Cardiac Catheterization in Eight Patients with Uncomplicated Pulmonic Stenosis*

Case number	Patient	Body surface area (M^2)	AP diameter of chest (cm.)	Pressures (mm. Hg)									Oxygen Consumption cc./min.		Oxygen Content of Blood (cc./liter)							A-V O_2 difference (cc./l.)	Cardiac output (l./min.)	Cardiac index (l./min./M^2)	Pulmonary vascular resistance (dynes-second-cm.$^{-5}$)	Pulmonary stenosis resistance (dynes-second-cm.$^{-5}$)
				Pulmonary "capillary"	Pulmonary Artery	PA_m	PA_{sm}	Right ventricle	RV_{sm}	RV_{sm}-PA_{sm}	Right auricle	Brachial artery	BMR	Expired air	Pulmonary artery	Right ventricle	Right auricle	Superior vena cava	Brachial artery	Oxygen capacity	Arterial → % O_2 saturation				
1	A. J.	1.75	19.0	9	16/8	13	15	80/8	56	41	6	120/73	240	211*	149	142	149	139	194	199	97	42*	5.0*	2.9	96	656
2	R. L.	1.94	19.0	13	33/14	19	20	33/1.99/1	63	43	1	[115/80]	217	249*	172	173	163	167	208	212	98	36*	6.9*	3.6	70	498
3	J. M.	1.73	17.0	13	28/10	17	19	85/0	30	11	2	[118/80]	191		156		152	144	218	221	99	62	3.1	1.8	129	284
4	T. M.	1.81	18.0	11	26/5	17	22	40/2	35	13	2	[130/65]	237		152	151	159	169	194	196	99	42	5.6	3.1	86	186
5	E. R.	1.54	17.5		22/15	—	17	35/6	24	7	6	[120/66]	170		152	149	137		184	186	99	32	5.3	3.4		106
6	W. P.	1.57	17.0	14	23/6	20	21	39/4	30	9	4	119/70	200	222*	136			119	167	172	97	31*	7.2*	4.6	67	99
7	S. C.	1.54	19.0	5	17/8	14	15	29/1	19	4		138/83	210	160*	139	136			177	180	98	35*	4.6*	3.0	122	69
8	W. H.	1.65	18.0	11	23/15	19	21	34/2	26	5	2	120/80	209	210*	169	172	160	157	213	207	97	37*	5.8*	3.5	110	69

[ ] Denotes cuff blood pressure

PA_m Denotes mean pressure in pulmonary artery

PA_{sm} Denotes mean systolic pressure in pulmonary artery

RV_{sm} Denotes mean systolic ejection pressure in right ventricle

* These figures were obtained from table 2 in which expired air, arterial, and mixed venous blood samples were obtained simultaneously for calculation of cardiac output. Cardiac outputs in Cases 3, 4, and 5 were determined as described elsewhere[3] and are reasonable approximations of the true values.

RESULTS

Diagnosis by Venous Catheterization

Pressure relationships: The relevant findings with regard to the diagnosis in each case are shown in table 1. The values represent the average mean during at least one respiratory cycle and in all instances these pressures were obtained as a continuous tracing during the with-

drawal of the catheter from the pulmonary artery into the right ventricle. The pressures are shown in table 1 and indicate the presence of pulmonic stenosis in each instance because of a significantly higher systolic pressure in the right ventricle than in the pulmonary artery[11]. When recorded in this fashion, such pressure differences indicate an obstruction between the right ventricle and pulmonary artery—by definition, pulmonic stenosis. Typical examples of such a pressure tracing are seen in figure 1. In one patient (Case 2), the tracing (fig. 1, *B*), though containing many artefacts, suggested the presence of a stenosis of the ostium infundibuli with a normal pulmonary artery valve. In other patients with the tetralogy of Fallot not included in this study (fig. 1, *C*)[10], the pressure tracings have suggested both a valvular stenosis and a stenosis of the ostium infundibuli, since the systolic pressure in the outflow tract of the right ventricle was greater than that in the pulmonary artery and less than that in the main chamber of the right ventricle. When there is no separate upper chamber to the right ventricle, it is doubtful if pressure tracings can distinguish a valvular from the fusiform type of infundibular stenosis.

Oxygen content of blood samples: In every instance, there was normal oxygen saturation of arterial blood, indicating the absence of any right-to-left shunt. It is believed that overriding of the aorta was not present in any instance because the systolic pressures in the right ventricle were not identical with those in the brachial artery[10]. It should be pointed out, however, that insignificant degrees of overriding cannot be entirely excluded. Samples of blood withdrawn from pulmonary artery, right ventricle, right auricle, and superior vena cava contained essentially the same amount of oxygen. In Cases 2, 5, and 8, the variation in oxygen content of blood samples between the right ventricle and right auricle was slightly in excess of the 0.9 volume per cent variation seen in normal individuals.[11] This suggests that small ventricular septal defects may have been present in these three patients, but if present they were of such small size as to have no functional significance. In Case 1, the difference in oxygen content of blood withdrawn from the pulmonary artery and right ventricle was 0.7 volume per cent, the upper limit of variation being 0.5 volume per cent in control groups.[11] Since the oxygen content of blood in the pulmonary artery and right auricle were the same, it seems likely that the ventricular sampling was truly representative and unlikely that arterial blood was really entering the pulmonary artery. In Case 6, samples were not withdrawn from the right ventricle and right auricle because of other studies being made at the same time. In this case, however, the variation in oxygen content of blood from the superior vena cava and pulmonary artery was within the normal range. In summary, therefore, it cannot be stated that a small septal defect, overriding of the aorta, or patent ductus arteriosus did not exist in these patients, but if such were present, they were of such small size as to have no functional significance. In this sense, therefore, these 8 cases are comparable to the 68 cases of anatomically uncomplicated pulmonic stenosis reported in the literature and reviewed by Greene and collaborators.[1]

Circulatory Dynamics at Rest and during Exercise

The results are shown in table 2. In general, oxygen consumption during the routine hospital metabolism was similar to that obtained during the resting state in our laboratory, indicating that the patients were in a relatively relaxed state. Ventilation, oxygen consumption, arteriovenous oxygen difference, cardiac output, and cardiac index were similar to our findings in individuals with normal cardiovascular systems.

The arteriovenous oxygen differences ranged from 31 to 62 cc./liter (table 1) and the cardiac index from 2.9 to 4.6 liters/minute/M^2. Determinations of mean pressure in the pulmonary artery gave values of 13 to 20 mm. Hg. These are well within the normal range.[10, 12] Mean pressure levels in the pulmonary "capillaries" were from 5 to 14 mm. Hg which are normal values.[7] The gradient between the pulmonary artery and pulmonary "capillaries" varied from 4 to 9 mm. Hg and the pulmonary vascular resistance varied from 67 to 129 dyne-second-cm.$^{-5}$. These were likewise normal.[7]

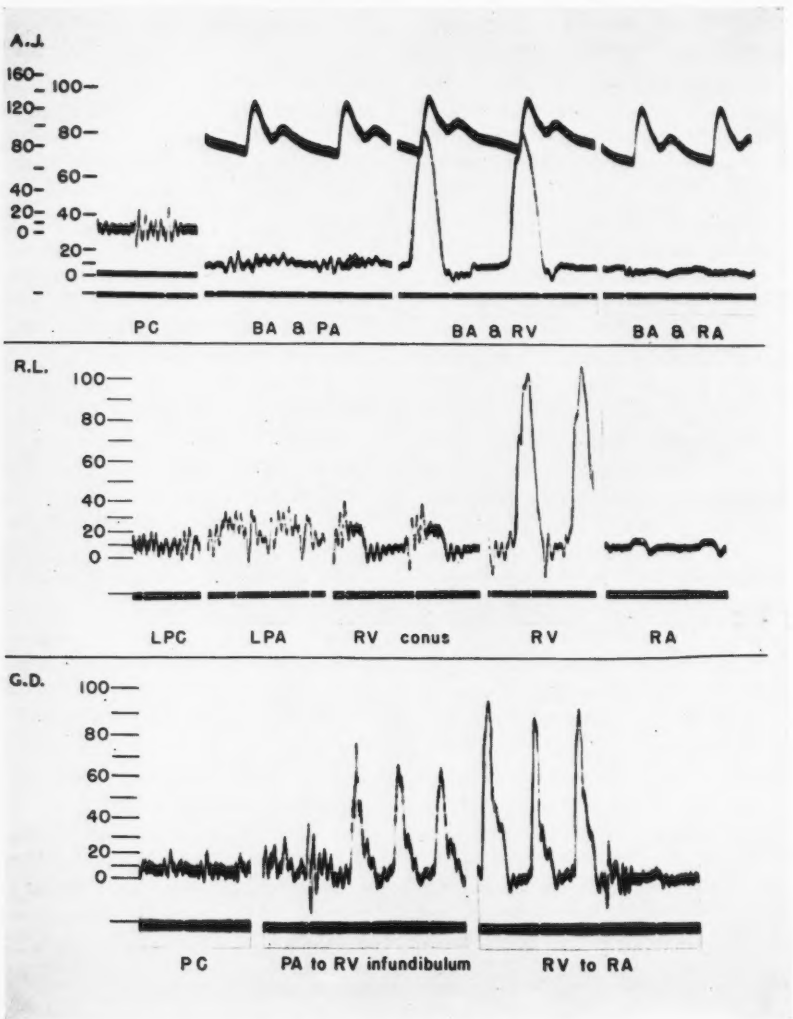

FIG. 1.—Pressure Tracings in Three Patients with Pulmonic Stenosis.

The upper tracing was recorded from Case 1. The upper heavy curve represents the pressure in the pulmonary "capillaries" (P. C.) on the left, and brachial artery (BA) in the remainder. The lower tracings were recorded through a catheter in the pulmonary artery, right ventricle, and right auricle. Note the elevated systolic pressure in the right ventricle as compared with that in the pulmonary artery.

The middle tracing was recorded from Case. 2 Note that the systolic pressures in the pulmonary artery (LPA) and upper part of the right ventricle (RV conus) appear to be identical while that in the main chamber of the right ventricle (RV) was markedly elevated. This suggests that the stenosis was at the ostium infundibuli rather than in the infundibulum itself or in the valve.

The lower tracing was taken from a patient with the tetralogy of Fallot. Note that the systolic pressure in the main chamber of the right ventricle (RV) is higher than that in the infundibular portion of the right ventricle (RV infundibulum) which in turn is higher than that in the pulmonary artery (PA). These findings suggest the presence of stenosis both at the ostium infundibuli and the valve.

Systolic pressures in the right ventricle, on the other hand, were distinctly higher than those in the pulmonary artery in all cases. The pressure levels in the right ventricle varied from 29/1 to 99/1 mm. Hg.

The pressure gradient between the right ventricle and the pulmonary artery during systole is normally zero and the pulmonary valve resistance is therefore normally zero as calculated by the Poisseuille equation. In these patients at rest, the pressure gradient varied between 4 and 43 mm. Hg and the stenosis resistance varied between 69 and 656 dyne-second-cm.$^{-5}$. In patients with the tetralogy of Fallot, the resistance has varied between 900 and 4000 dyne-second-cm.$^{-5}$.[10] The calculation of stenosis resistance gives a much better indication of the degree of stenosis than pressures alone, and all of our patients may be considered to have had pulmonic stenosis of relatively mild degree.

Under conditions of exercise and with an obstruction to the outflow of blood from the right ventricle, it might be predicted that the following physiologic adjustments would occur: (1) rise in the right ventricular pressure in an attempt to increase flow, and (2) marked increase in the arteriovenous oxygen difference in proportion to the cardiac output. The latter represents a circulatory adjustment to the inability of the heart to increase its output materially whether due to obstruction to flow or to myocardial insufficiency. The data set forth in table 2 indicate that mild to moderate exercise increased the right ventricular pressure, in one instance from 99/2 to 130/10 mm. Hg and in a second patient from 39/4 to 77/20. That the increase in pressure was adequate to overcome the obstruction and provide for an adequate blood flow is demonstrated by a normal increase in the cardiac output that occurred (5 to 12 liters) and without any unexpected increase in the arteriovenous oxygen difference. Further, there was no indication that a failure to increase cardiac output occurred in those patients with a high right ventricular pressure.

These findings further suggest that we observed patients with a relatively mild degree of pulmonic stenosis and with an adequate right ventricle. If exercise had been pushed to the

TABLE 2.—*Effect of Exercise on Circulatory Dynamics of Five Patients with Uncomplicated Pulmonic Stenosis*

Case number	Patient	State	Bicycle resistance at 56 RPM (lbs.)	AP diameter of chest (cm.)	Pressures (mm. Hg)						Respiratory rate (per min.)	Vital capacity (liters)	Ventilation (liter/min.)	Ventilation equivalent	Oxygen Consumption (cc./min.)		Blood Oxygen				A-V O_2 difference (cc./liter)	Cardiac output (liter/min)	Cardiac index (liter/min./M^2	Pulse rate	Stroke output (cc.)	Pulm. V.R. dyne.-sec.-cm.$^{-5}$
					Pulmonary "capillary"	Pulm. artery	PA − PC gradient	Right ventricle	Right auricle	Brachial artery					BMR	Expired air	Pulm Art. Content (cc./l)	Brachial Artery Content (cc./l.)	Brachial Artery Capacity (cc./l.)	Brachial Artery Saturation (%)						
1	A.J.	Rest	0		9	13	4	80/8	9	80	12	3.6	6.4	33	240	210	152	194	199	97	42	5.0	2.9	66	76	64
		Exercise #1	2	19	13	15	2	—	—	88	24	3.8	12.5	41	—	509	125	196	198	98	71	7.2	4.1	78	92	22
		Exercise #2	8		—	15	—	—	9	80	28	—	18.6	46	—	864	101	194	198	98	93	9.3	5.2	104	89	—
2	R.L.	Rest	0		13	19	6	99/2	9	—	12	—	5.4	46	217	249	172	208	212	98	36	6.9	3.6	70	98	70
		Exercise #1	2	19	12	23	11	—	—	—	14	—	15.6	61	—	957	143	—	—	—	—	—	—	120	—	—
		Exercise #2	11		—	27	—	130/10	10	—	18	—	25.3	52	—	1312	121	—	—	—	—	—	—	148	—	—
6	W.P.	Rest	0		14	20	6	39/4	8	78	16	2.5	6.0	37	200	222	136	167	172	97	31	7.2	4.5	74	97	67
		Exercise #1	2	17	—	20	—	—	—	86	24	2.5	16.2	39	—	637	103	172	174	99	69	9.2	5.8	112	82	—
		Exercise #2	7		—	20	—	77/20	20	97	32	—	28.6	36	—	1025	84	169	175	97	85	12.1	7.6	118	103	122
7	S.C.	Rest	0	19	7	14	7	29/1	—	105	17	2.9	5.7	28	210	160	142	177	180	98	35	4.6	3.0	72	64	89
		Exercise #1	2		6	13	7	—	—	—	25	2.8	9.6	42	—	401	106	177*	180	98*	74*	5.4	3.5	104	52	—
8	W.H.	Rest	0	18	11	19	8	34/2	2	93	20	3.4	6.4	34	209	210	162	199	207	96	37	5.8	3.5	88	66	110
		Exercise #1	2		11	18	7	—	3	119	24	3.4	16.5	31	—	503	132	203	217	94	71	7.1	4.3	92	77	79

PA = pulmonary artery; PC = pulmonary "capillaries"; Pulm. = pulmonary; V.R. = vascular resistance.

* Indicates an assumed value, since arterial oxygen saturation remained unchanged by Millikan Oximeter.

limit, differences from the normal would have undoubtedly become apparent.

The determination of the right ventricular pressure during exercise may be accompanied by frequent premature ventricular beats, ventricular tachycardia or fibrillation, and is, therefore, an extremely dangerous procedure. Such an alarming complication (ventricular tachycardia) occurred in one patient (Case 6) and disappeared when the catheter was withdrawn into the right auricle. In this individual there was a fall in the right ventricular systolic pressure and a rise in the diastolic pressure, and at least for several minutes the pressure was elevated in the right auricle. In view of no history of limitation even with strenuous exertion, it seems likely that this elevation of right ventricular diastolic and right auricular pressures was attributable to the ventricular tachycardia. The remainder of the right auricular pressures were within normal limits.

The right ventricular pressure can be measured safely during exercise by using a double lumen catheter,[13] with the proximal outlet in the right ventricle and distal outlet in the pulmonary artery.

In summary, except for the increased resistance at the pulmonary valve or infundibulum and the abnormal rise of pressure in the right ventricle, all findings on mild and moderate exercise were within normal limits. This again emphasizes the mildness of the pulmonic stenosis of this particular group of patients and the good state of compensation of their right ventricle.

Clinical Aspects

In table 3 will be found the salient clinical findings in our cases. In no instance was a history of German measles or other exanthematous disease elicited among the mothers of these patients during pregnancy.

Six of the 8 patients were males. In the literature, there has been no sex predisposition.[1]

The ages of the patients varied from 11 to 26. The younger age group is not represented because there is no pediatric service at the Peter Bent Brigham Hospital. In the literature, the age of patients at death has varied between 5 months and 75 years, the average age at death being 26 years.[1] Although pulmonic stenosis has been stated to predispose to tuberculosis,[14] such a relationship has not been striking in the reported cases of pure pulmonic stenosis

TABLE 3.—*Vital Data of Eight Cases of Uncomplicated Pulmonic Stenosis Recognized by Venous Catheterization*

Case number	Patient	Sex	Age	History						Physical examination									Roentgen examination				Electrocardiographic findings								
				Murmur first noted (years)	B. endocarditis	Cyanosis	Restricted activity	Exertional dyspnea	Exertional fatigue	Development	Heart sounds			Heart murmurs				Systolic thrill	Heart size	Pulmonary artery		Right ventricle	Right auricle	P-R interval (second)	QRS (second)	Mean electrical axis	Axis deviation index	R. V. hypertrophy	Electrical position	Intrinsic deflection—sec.	
														Systolic		Diastolic															
											S_1	A_2	P_2	Location†	Grade	Location†	Grade			Size	Pulsation									Right ventricle	Left ventricle
1	A. J.	M	23	5	o	+	+	+	+	N	N	N	N	3	4	o	o	+	N	+++	+	N	N	0.15	0.08	+114°	−13	*	Vertical	0.06	0.03
2	R. L.	M	26		+	o	o	o	o	+	N	N	+	3	4	o	o	+	+	+		+	++	0.15	0.09	+103°	+12	+	Intermediate	0.05	0.03
3	J. M.	M	22		o	+	+	±	o	N	o	o	o	2	6	o	o	+	N	N	+	+	+	0.17	0.10	+129°	−17	+	Vertical	0.03	0.02
4	T. M.	M	14		o	+	o	+	+	+	+	N	+	3	3	o	o	o	N	++		N	N	0.14	0.10	+105°	−20	*	Vertical	0.05	0.04
5	E. R.	F	19	4	o	o	o	o	o	N	N	N	N	4	3	o	o	o	N	N		N	+	0.16	0.12	−12°	+8	o	Intermediate	0.03	0.05
6	W. P.	M	11	2	o	o	o	±	o	+	N	N	N	3	5	o	o	+	N	++	++	N	+	0.12	0.06	+90°	−11	*	Vertical	0.04	0.03
7	S. C.	F	15	7	o	o	o	o	o	N		N	+	2&3	3	o	o	o	N	+		N	N	0.14	0.10	+25°	−11	o	Intermediate	0.02	0.03
8	W. H.	M	13	1	o	o	o	±	o	N		N	N	2&3	2	2&3	2	o	N	+++	+	N	N	0.16	0.08	+59°	+4	o	Vertical	0.02	0.04

o = absent, + = present or increased, N = normal, † = point of maximal intensity in left intercostal space, * = persistent incomplete right bundle branch block, R. V. = Right Ventricle, B = Bacterial.

In no case was there a history of cyanosis at birth, tuberculosis, rheumatic fever, hemoptysis, chest pain, orthopnea, or edema. On physical examination, none had cyanosis, clubbing, cardiac arrhythmias, or signs of congestive heart failure. By x-ray and fluoroscopy, the left ventricle, left auricle, and hilar vascular markings appeared normal in each case.

or in our small experience. Greene and associates[1] have raised serious doubts about any cause and effect relationship.

None of our patients were "blue" babies; none had a history of rheumatic fever; none had tuberculosis by history or roentgenogram of the chest; none had hemoptyses; and one with stenosis of the ostium infundibuli (Case 2) had had subacute bacterial endocarditis cured with penicillin at the age of 25. Having had no limitation of activity prior to this infection, there was no way of telling whether he had improved as a result of enlargement of the stenotic opening as apparently occurred in a case reported by Pollack and associates.[5] In the 68 cases reviewed by Greene and coworkers,[1] 26 died of congestive heart failure, 10 of tuberculosis, and 8 of subacute bacterial endocarditis.

Four of our patients gave a history of cyanosis on exertion or exposure to cold which could not be confirmed at the time of physical examination and in all cases the arterial oxygen saturation was normal (table 1). No clubbing was observed in any of the patients. In the 68 cases reviewed by Greene and collaborators,[1] at least 28 were cyanotic and 4 were said to have clubbing of the fingers. There has been considerable interest expressed in the late development of cyanosis in these patients. To the attending physician it suggests the complication of some right-to-left shunt. Greene and co-authors[1] felt that evidence for the existence of cyanosis in these individuals was not convincing. We have seen such a case with closed septa at postmortem examination (not included in this report) in whom cyanosis was a prominent feature. All observers[1, 15–19] have been of the opinion that the cyanosis in these individuals is due to a slow peripheral circulation with a resultant de-oxygenation of blood in the tissues. This leads to a low venous oxygen and a type of cyanosis which Peacock[20] first pointed out was more reddish-blue than blue. With this observation we are in agreement. Arnett and Long[18] found the arterial oxygen saturation to be 94.7 per cent in a cyanotic patient with pulmonic stenosis and a foramen ovale considered to be functionally closed. Perhaps the simplest test for excluding a right-to-left shunt in these individuals is the circulation time as Garrison and Feldt[15] suggested. A circulation time of 5 or 6 seconds suggests a right-to-left shunt; with a prolonged circulation time, the cyanosis would not be on a shunt basis. From studying case reports[15–17, 20–25], it is apparent that the cyanosis appears at about the time that symptoms and signs of heart failure appear.

All of our patients were normally developed. Three could be described as husky. Three had no physical limitations even on extreme activity, three were limited only on extreme exertion, and two on moderate exertion. None had symptoms at rest and none gave any history of progressive decrease in exercise tolerance. Since all of these patients were doing well, they do not represent a true cross section of this disease. In 13 carefully described cases in the literature who developed heart failure[16, 17, 20–22, 24 (Cases 4, 6, 8–10) 26–28] the type of failure encountered was almost exclusively that of chronic congestion of the viscera with hepatomegaly, ascites, and edema. In none was there evidence of pulmonary congestion except agonally or where pulmonary or left ventricular pathology could have been responsible.[21, 24 (Case 8), 25, 26, 28] Precordial pain has been observed by us frequently in patients with the tetralogy of Fallot, but none of our patients with simple pulmonic stenosis complained of chest discomfort, although it has been reported by others.[16, 17, 21]

Physical examination of our patients showed that they had a normal development. This would obviously be a variable finding, depending on the severity of the stenosis during the growing period. In severe cases, growth and development have been reported to be retarded in a number of instances.[15–17, 22, 23, 24 (Cases 7–9)]

The heart may or may not be enlarged clinically depending on the severity of the pulmonic stenosis and its duration. Although the rhythm was regular in our cases, ventricular premature beats,[23] auricular fibrillation,[16] and auricular flutter[16] have been reported. In all of our cases, there was a harsh systolic murmur which was maximal in the second, third, or fourth intercostal space just to the left of the sternum. It varied in loudness from Grade 2 to Grade 6. Currens, Kinney, and White[24] believed

that there was a correlation between the intensity of the murmur and the degree of stenosis, and this has, in general, been our experience (table 3). Blackford and Parker[23] published the first heart sound tracings of the murmur in pure pulmonic stenosis. Figure 2 shows examples

disease) or atrial septal defect. Although it has been suggested that when located in the second left intercostal space the murmur was more characteristic of a valvular stenosis and when lower of an infundibular stenosis, Guinsbourg[9] was unable to differentiate the type of stenosis

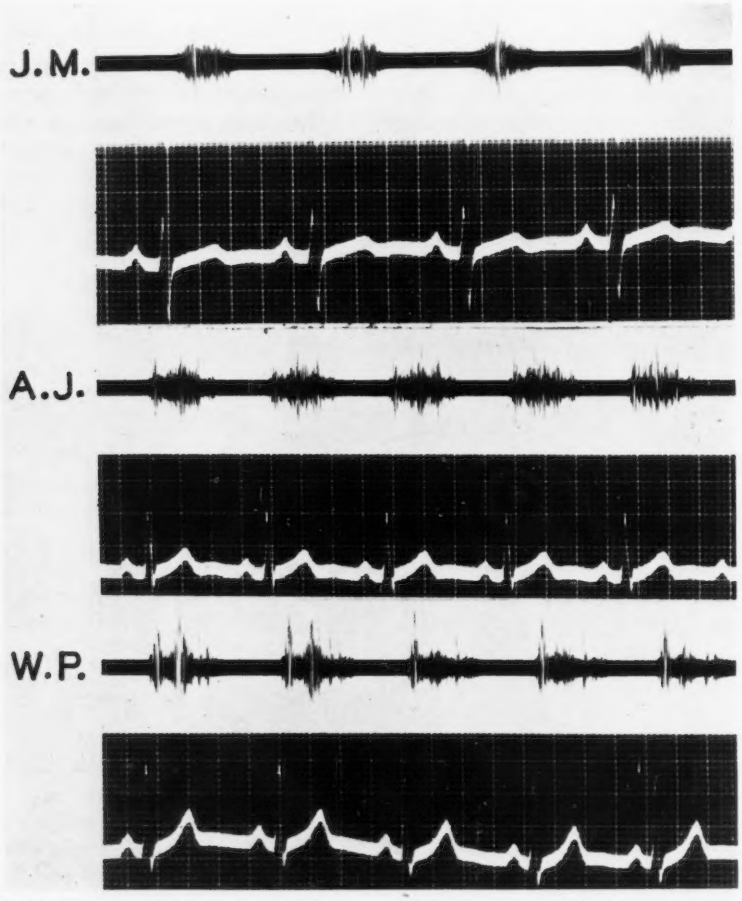

FIG. 2.—Heart Sound Tracings in the Pulmonic area of Cases 3, 1, and 6. Note that the systolic murmur is loudest in mid-systole.

from several of our patients. It usually has a "diamond-shape"; that is, it is loudest in mid-systole. Such a "shape" is not pathognomonic for this condition, however, since it has been found in other disorders and is not uniformly found in pulmonic stenosis. Its location likewise has not served to differentiate this murmur from that of ventricular septal defect (Roger's

by the location of the murmur. The murmur is usually but not always accompanied by a palpable thrill as Laubry and Pezzi[30] emphasized. It may be widely transmitted over the precordium and back, or its transmission may be fairly limited. Laubry and Pezzi[30] attached considerable diagnostic importance to the lack of transmission above the clavicle, and this has

in general been our experience and that of Brown.[2] Currens, Kinney, and White,[24] however, stated that the murmur was characteristically transmitted into the neck. The pulmonic second may be normal, decreased, or increased in intensity. In 4 cases of pulmonic stenosis with elevated pressures in the right ventricle on venous catheterization, Greene and co-workers[1] foun the pulmonic secon sound to be normal or decreased. In 4 cases with a higher pressure in the right ventricle than in the pulmonary artery in whom the right ventricular pressure was still within the range of normal, the pulmonic second sound was increased. These authors considered the patients to have idiopathic congenital dilation of the pulmonary artery. In our limited experience the pulmonic second sound has been loudest in those with the mildest stenosis (tables 1 and 3) but this rule does not hold in patients with the tetralogy of Fallot.[10] Currens, Kinney, and White[24] expressed the opinion that the second sound in the pulmonic area was probably derived from closure of the aortic valve in these cases. In one of our patients, a soft blowing, short, early diastolic murmur was noted, presumably indicating some insufficiency of the pulmonic valve. Pulmonic diastolic murmurs have been reported by others in cases of pure pulmonic stenosis.[16, 22, 23, 24 (Cases 4, 8, and 10), 25, 26]

Roentgen Examination of the Heart

The roentgenologic aspects of uncomplicated pulmonic stenosis have been well described.[2, 30–32] In 1918, Vaquez and Bordet[31] pointed out three cardinal x-ray manifestations of pure pulmonic stenosis: (1) prominent right auricle and right ventricle; (2) normal left auricle and left ventricle; and (3) prominent pulmonary artery. To this, we would add a fourth: normal or decreased pulmonary (hilar) vascular markings.

Twelve autopsied cases of simple pulmonic stenosis with roentgenographic studies have been reported.[15–17, 23, 24 (Cases 4, 7, 8, and 10), 25–28] In 10, the heart was considered to be enlarged and in 2[15, 24 (Case 4)] of normal size. In seven, the pulmonary artery was stated to be prominent.[15, 17, 23, 24 (Cases 4 and 10), 25, 27] In one,[17] both the right auricle and left ventricle appeared to be enlarged. In other cases, the size of the various chambers was not described.

Our 8 cases were studied fluoroscopically and films were taken in the posterior-anterior, right anterior oblique, and left anterior oblique positions. Postero-anterior kymograms were obtained in some. Measurements of heart size in accordance with the Ungerlieder and Clark[33] standards revealed cardiac enlargement in only one of the patients (Case 2) with recent subacute bacterial endocarditis. Figure 3 illustrates the cardiac silhouette in several of our cases. Four of our cases showed apparent enlargement of the right auricle, slight in 3, and moderate in one. Slight enlargement of the right ventricle was noted in 2 of our cases, both associated with right auricular enlargement. Left auricular enlargement was present in none. The left ventricle appeared enlarged in one patient (Case 2) but the electrocardiogram showed right ventricular hypertrophy. In six cases there was prominence of the pulmonary artery. In 2 cases, this prominence was marked, in 2 moderate, and in 2 slight. The degree of enlargement of the pulmonary trunk appeared to bear no relationship to the degree of stenosis. In 4 cases, there was an increased amplitude of pulsation of the pulmonary artery fluoroscopically or by kymogram. Fluoroscopically and by plain x-ray film, the appearance of the intrapulmonary vascular markings was normal. From published x-ray studies on autopsied cases,[17, 25, 27, 32] this has likewise been the case. In no instance was there a hilar dance and in none of our cases were the vascular markings of the lung actually decreased in contrast to the usual finding in the tetralogy of Fallot where pulmonary blood flow is reduced to a much greater extent than in the cases here reported.

In our experience, therefore, two of the three criteria set forth by Vaquez and Bordet[31] were constant, that is, normal left auricle and left ventricle, and in six of our eight cases a prominent pulmonary artery. With regard to the right auricle and ventricle, however, enlargement of these chambers was not always apparent in mild cases either by fluoroscopy or by electrocardiogram. In more severe cases, en-

largement was readily apparent. The fourth characteristic—normal or decreased hilar vascular markings—was a uniform finding and is of considerable differential significance.

twice.[16, 23] Right ventricular hypertrophy was reported in 2 of the cases of Pollack and associates[5] in which the diagnosis was made by cardiac catheterization.

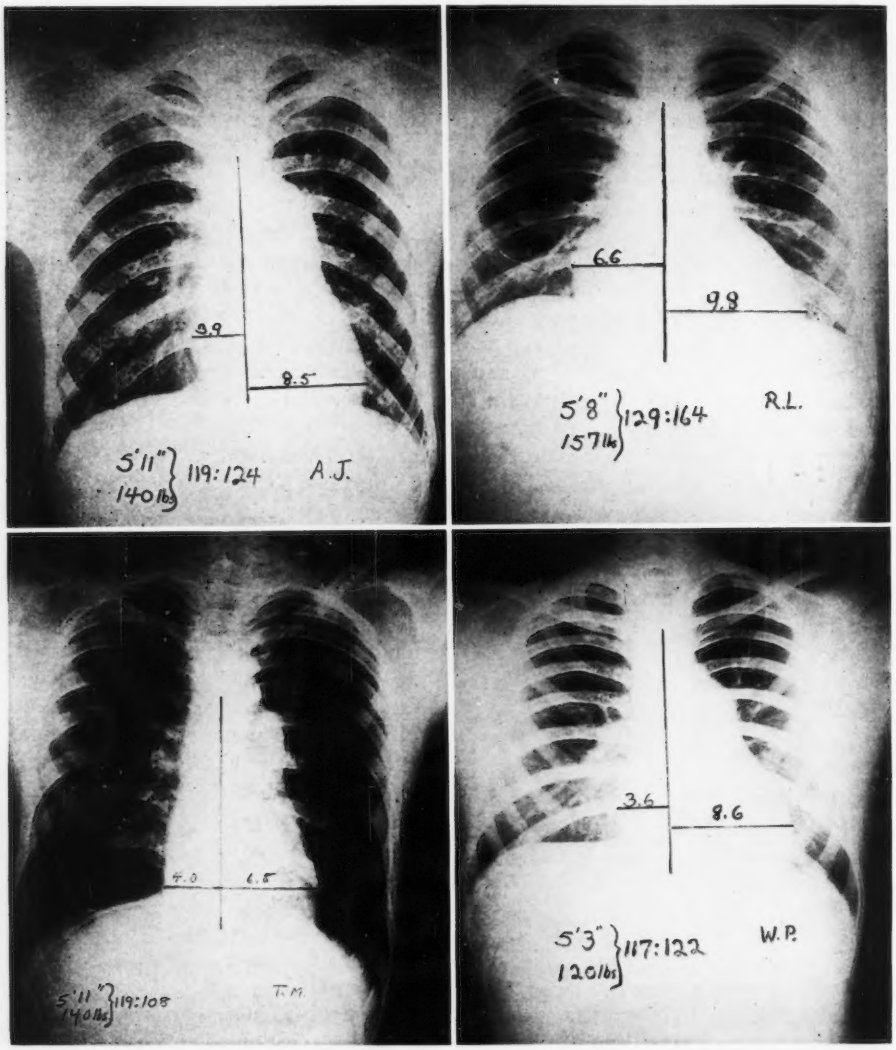

FIG. 3.—PA Roentgenograms of Cases 1 (upper left), 2 (upper right), 4 (lower left), and 6 (lower right). Note the prominent pulmonary artery and normal pulmonary vascular markings in each.

Electrocardiographic Findings

Right axis deviation has been the usual electrocardiographic finding in simple pulmonic stenosis[15, 17, 24 (Cases 4 and 9), 25, 27] and right bundle branch block has been reported

At least twelve leads were taken in our 8 cases, including the three standard leads, three unipolar limb leads (augmented technic with resistances retained), and six unipolar chest leads after the manner of Wilson.[34, 35] In selected

cases additional leads including the ensiform lead V_E and one or more leads to the right of V_1 (V_{3R} and so forth) were also taken. In all 8 cases the duration of the P-R and QRS intervals was measured and the mean electrical axis and White-Bock axis deviation index calculated. An axis deviation index of plus 20 is very good evidence of left ventricular hypertrophy; of minus 13 or less, fairly good evidence of right ventricular hypertrophy. This determination gives weight to the absolute magnitude of the various components of the QRS complex and thus probably represents the actual electrical effects of each ventricle much better than does the mean electrical axis. On the basis of the electrical potentials at the left shoulder and left leg in their relation to the precordial potentials[34], the electrical position of the heart was then determined. It is worthy of emphasis that this may or may not correspond to the anatomic axis of the heart. On the basis of the criteria of Wilson,[35] it was then decided from the precordial potentials whether right or left ventricular hypertrophy was present. Finally, the ventricular intrinsic deflections were measured over the right and left ventricle (usually from Leads V_1 and V_6, respectively) correctly to the nearest 0.01 second. This measurement signals the moment of electrical activation of the myocardial tissue immediately underlying the precordial electrode and this was taken as the point of origin of the final rapid downward deflection of the ventricular complex.

The results of this study are shown in table 3 and illustrated in figures 4 and 5. Five of the 8 individuals showed a mean electrical axis of plus 90 or more and on that basis would be considered to have right axis deviation. In 3 cases the axis deviation index was minus 13 or less; these were the three whose mean electrical axes were the furthest to the right. In the remaining 5 cases the axis deviation index lay within the normal range of minus 13 to plus 20. The electrical position of the heart was vertical in 5 cases and intermediate in 3.

In Cases 1 and 2, tall R waves were recorded at the right shoulder (Lead aV_R) that almost equaled the magnitude of the preceding Q wave. In four other cases the R wave in aV_R was more prominent than usual. This may be the result of posterior rotation of the left ventricle which thus casts its electrical shadow at the right shoulder[36] or of late electrical activation of the base of the outer wall of the right ventricle which may be in relation to the right shoulder.[37, 38]

The intrinsic deflection was inscribed later over the right than the left ventricle in 5 cases. In 2 of these patients (Cases 2 and 3) the diagnosis of right ventricular hypertrophy and in 3 (Cases 1, 4, and 6) on the basis of a secondary R wave (R′), the diagnosis of incomplete right bundle branch block seemed justified. Since persistent incomplete right bundle branch block is also very good evidence of right ventricular hypertrophy[37] the electrocardiographic diagnosis of right ventricular hypertrophy was made in all five cases with late intrinsic deflections over the right ventricle.

In 3 patients (Cases 5, 7, and 8), the intrinsic deflections of the ventricular complex were inscribed earlier over the right than the left ventricle. In 2 of these patients (Cases 7 and 8) the QRS duration was 0.08 and 0.10 second, respectively. In these cases the tracings were interpreted as normal. From their hemodynamics (table 1), these patients had pulmonic stenosis of mild degree. In the third patient (Case 5) the QRS duration was 0.12 second, the R waves were tall in Leads V_5, V_6, and V_7, the RS-T segment depressed and T waves biphasic in V_5, and a small Q wave was present in V_7. Although the evidence is not conclusive, the tracings in this case were regarded as very suggestive of left ventricular hypertrophy with intraventricular block.

Tall, sharply peaked P waves in Leads II and III ("P pulmonale") have long been regarded as collateral evidence of right ventricular hypertrophy. In only one case in this group were such P waves recorded. This was in Case 3 in whom P_2 measured 3.5 and P_3 2.5 millimeters. In this case the P wave was directed downward at the right shoulder (aV_R) and left shoulder (aV_L) and was upright at the left leg (aV_F). The large voltage of the P waves was clearly the algebraic summation of these effects $\left(\text{Lead II equals } \frac{2(aV_F - aV_R)}{3} \text{ and}\right.$

Lead III equals $\frac{2(aV_F - aV_L)}{3}$), and not the result of prominent P waves at the left leg.

The most frequent single finding in this group of cases was late electrical activation of the right ventricle, whether due to right ventricular hypertrophy or to incomplete right bundle branch block or to both. Considering

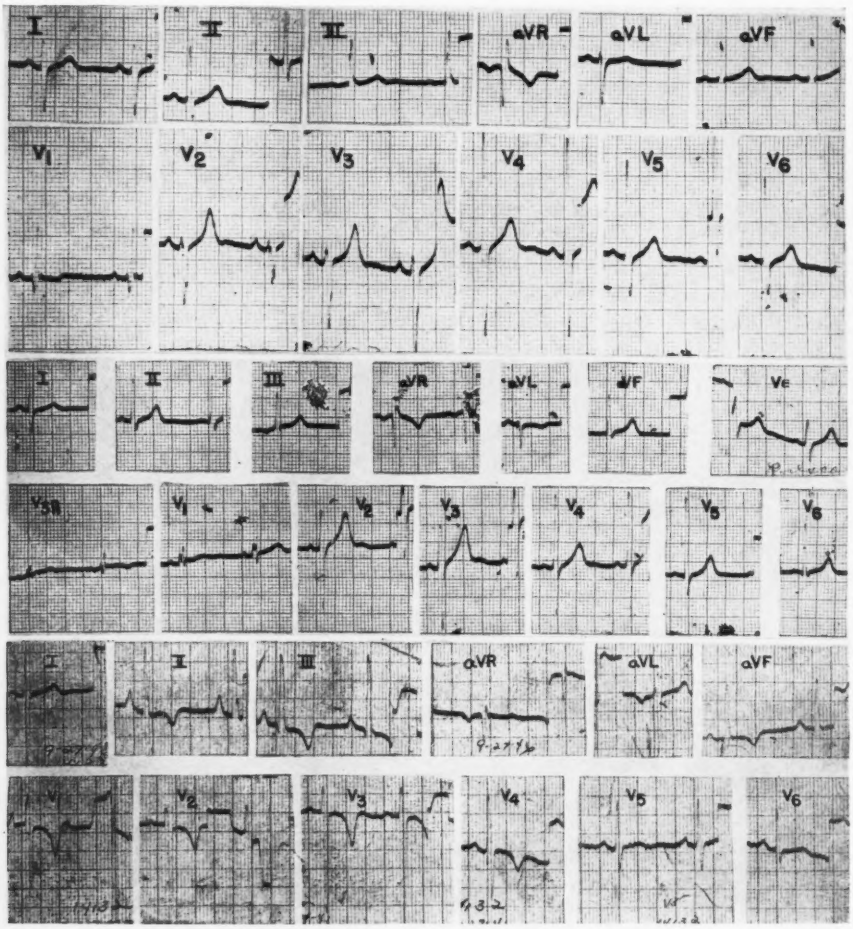

FIG. 4.—Electrocardiograms in Three Patients with Pulmonic Stenosis.

Upper two tracings (Case 7) show right axis deviation, tall R wave in aV_R and late intrinsic deflection in V_1 with tall R wave in V_1 compatible with incomplete right bundle branch block. Heart in vertical position.

Middle two tracings (Case no. 6) show an M-shaped QRS Complex in V_{3R} and V_1 suggesting incomplete right bundle branch block. The ensiform Lead V_E here resembles a V_F and records the potential of the posterior aspect of the heart.

Lower two tracings (Case 3) reveal a tall R wave in V_1 (exceeding the R wave in V_2), depressed RS-T segment in V_1 and V_2 and inverted T wave inV_1 through V_4. Lead V_{3R} would have been helpful in this case. Tall P_2 and P_3 ("P pulmonale") are a consequence of an inverted P wave in Leads aV_R and aV_L and of the upright P wave in aV_F and hence are explained by the vertical position of the heart.

Here then the prominent P waves were the result of the position of the heart.

persistent incomplete right bundle branch block an evidence of right ventricular hypertrophy, this diagnosis could be made in five of the eight cases. Right axis deviation, as manifested by a mean electrical axis to the right of plus 90 degrees, was noted in most cases but this change is nonspecific and can be produced merely by a vertical position of the heart. An axis deviation index of less than minus 13 was less frequently noted. Prominent P waves in Leads II and III were observed only once and in that case could likewise be explained as the result of the vertical position of the heart. But in the last analysis it was the study of multiple precordial leads which gave the decisive evidence for the diagnosis of right ventricular hypertrophy.

In view of the absence of correlative anatomic data, a discussion of the controversial subject of the stress-strain or pressure-hypertrophy relationships is deliberately avoided here. However, in the five cases of right ventricular hypertrophy as determined electrocardiographically, it can be assumed that the increased right ventricular pressure recorded manometrically was of sufficient duration and degree to have led to right ventricular hypertrophy.

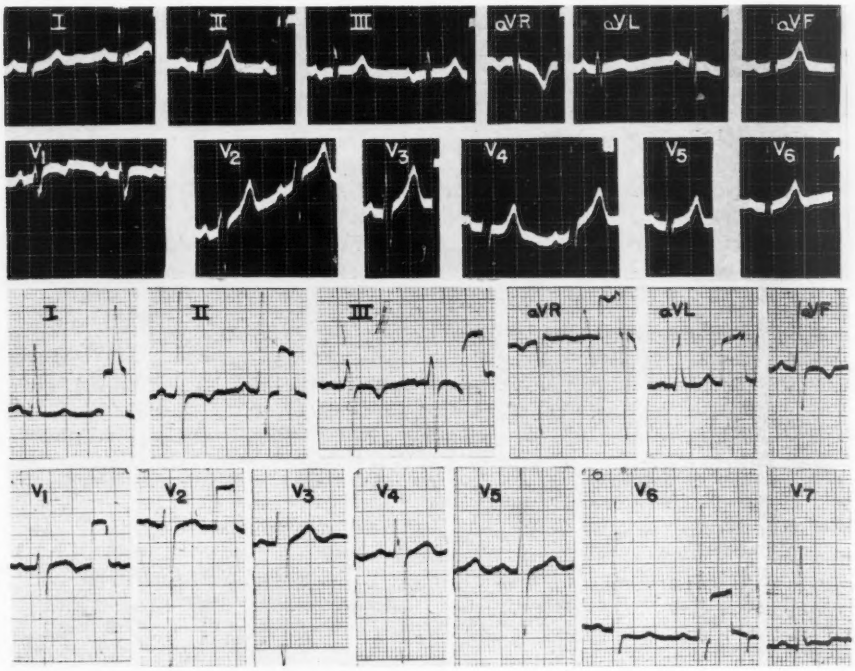

FIG. 5.—Electrocardiograms in Two Patients with Pulmonic Stenosis
Upper two tracings (Case 8) are normal.
Lower two tracings (Case 5) show tall R waves, depressed S-T segment and biphasic T waves in V_6 suggesting left ventricular hypertrophy.

DISCUSSION

Frequency: Simple pulmonic stenosis has been considered a rarity and yet on the basis of venous catheterization we have found it to be relatively common. Keith,[39] in his classic analysis and interpretation of 272 congenital hearts in 1909, found pulmonic stenosis, simple or with associated defects, in 128 or 45 per cent. Although he was primarily interested in studying the developmental aspects of these abnormalities rather than in pointing out the frequency of specific lesions, it is apparent that

uncomplicated pulmonic stenosis was not considered by him to be rare. In 19 cases of stenosis of the ostium infundibuli, he found that 9 had an associated ventricular septal defect, 3 patent ductus arteriosus, and 2 patent foramen ovale. By implication, the remaining 5 of the 19 were unassociated with other defects. In 44 cases with a fusiform type of infundibular stenosis, he stated that an interventricular foramen was present in over half and that in a few, patent ductus arteriosus or patent foramen ovale was present. Again, it is implied that the uncomplicated lesion was not rare. Since then, all writers have stressed its rarity. Abbott,[19] for example, made note in her Atlas of only 9 cases among 1,000 congenital hearts. It is not clear at this time why there is such a discrepancy between pathologic findings and physiologic evidence of obstruction between the right ventricle and pulmonary artery as indicated by pressure tracings. One wonders if mild pulmonic stenosis, especially of the fusiform variety, would be readily recognized by routine postmortem examination. Brown[2] has suggested that in cases of subaortic stenosis the anatomic condition can be studied by introducing a rubber condom, filling it with plaster of Paris, and thus obtaining a cast of the aorta and the stenotic area. This might be the best way of studying the fusiform type of infundibular pulmonic stenosis. Stenosis of the valve and of the ostium infundibuli should afford no difficulty in recognition. It seems doubtful if the reason for the frequency of pulmonic stenosis by venous catheterization and its rarity at postmortem examination will be clarified until careful postmortem examinations of these hearts are carried out.

Pathologic anatomy: Keith[39] was the first to classify the types of pulmonic stenosis that occur congenitally and little pertaining to this discussion has been added since 1909. There are two distinctly different types, the valvular and the infundibular, and the latter may be of two sorts.

In valvular stenosis, there is a fusion of the valve leaflets which form a dome with a central aperture of variable size.

The second type is the so-called infundibular (or conus) stenosis in which the stenotic area is in the right ventricle rather than in the valve. Two types of infundibular stenosis were described by Keith and, because of present-day surgical implications, these two types should perhaps be borne in mind, although they apparently represent variations on a common theme. Keith pointed out that the mammalian heart consisted of the sinus venosus, the auricles, the ventricles, and the bulbus cordis. Just as the sinus venosus becomes incorporated in the right auricle, the bulbus cordis becomes included in the right ventricle forming the part known as the infundibulum, conus, or outflow tract. A large number of the common malformations of the human heart are due to arrest of the process which ends in the incorporation of the bulbus cordis into the ventricles. Thus infundibular pulmonic stenosis has, as its counterpart on the left, subaortic stenosis.

In the first type of infundibular stenosis (fusiform type), there is a narrowing of the infundibular cavity to such an extent as to produce an obstruction to blood flow. This narrowing is located between the main chamber of the right ventricle and the valve and according to Keith is due to arrest in its developmental expansion. Fusion of the pulmonary valve leaflets were observed rather frequently in Keith's hearts. The narrowed area in pulmonic stenosis is sometimes striking. In the patient reported by Currens, Kinney, and White,[24 (Case 7)] the diameter of the pulmonary ring was only 1.5 mm. and in at least 3 other reported cases it was only 2.0 mm.[12, 15, 17]

Limitations of venous catheterization in distinguishing these three types of pulmonic stenosis have already been discussed. Angiocardiography might serve this purpose better.[40]

In 68 autopsied cases of pure pulmonic stenosis reviewed by Greene and coworkers,[1] the right ventricle was enlarged in all but 5. The right auricle is often enlarged[16, 17, 22, 23, 24 (Cases 9 and 10), 25, 27] but may be of normal size.[15, 24 (Cases 4 and 6)] Occasionally enlargement of the left ventricle has been described.[15, 28] In each instance, however, there were other causes for the enlargement of the left side of the heart. In no instance to our knowledge has the left auricle been described as enlarged. The lungs

have been reported to be singularly free of evidence of chronic passive congestion at autopsy[15–17, 20, 22–24, 26–28] and in three instances[20, 24 (Case 8), 25] in which this finding has been described, it appeared from the description to be an agonal complication. Chronic passive congestion of the viscera is the usual finding in those dying in heart failure[16, 17, 20, 24 (Cases 4, 7–10), 25, 27] and in this respect tallies well with the clinical findings.

In the 68 autopsied cases reported by Greene and associates,[1] the pulmonary artery was enlarged in 33 instances, was of normal size in 19, and in the remainder of the cases, its size was not mentioned. In most of our own cases x-ray examination revealed enlargement. Considerable interest has attached to the enlargement of the pulmonary artery in these and in other cases with associated defects. Peacock[20] stated that the pulmonary artery was enlarged in simple pulmonic stenosis and was usually small when pulmonic stenosis and ventricular septal defect were associated. Bernard[41] attributed the poststenotic dilatation to stasis of blood with increased pressure beyond the point of stenosis. Solmon[42] disagreed, stating that the pressure should be decreased beyond the point of stenosis. He believed that concomitant tuberculosis produced a loss of elasticity and in turn a dilatation of the vessel. Laubry and Pezzi[30] attributed poststenotic dilatation to malnutrition of the vessel walls, Potain and Rendu[43] to a concomitant endarteritis resulting from malnutrition of the walls of the pulmonary artery, Frerichs[44] and Currens, Kinney, and White[24] to an associated pulmonic insufficiency, and Paul[45] to congenital weakness of the vessel. Cavina[46] was the first to exclude this latter possibility by producing pulmonary stenosis experimentally in puppies. The pulmonary artery dilated beyond the point of obstruction. The media and adventitia became thinned and the intima became hyperplastic. This is the usual histologic change that has been described in human cases.

In our experience, dilatation of the pulmonary artery is rare in patients with the tetralogy of Fallot and common in those with simple pulmonic stenosis. The main differences in these two groups of patients are that the blood flow, mean pressure, and pulse pressure in the pulmonary artery are low in the tetralogy group and are normal or near normal in those with simple pulmonic stenosis, at least in the eight patients here reported (table 1). Whatever the explanation of the poststenotic dilatation, it does not usually extend beyond the bifurcation of the pulmonary artery. In some, the vessel walls are of normal thickness but in others they become hypoplastic and as thin as tissue paper.[10]

Recently, Greene and coworkers[1] reported 4 cases of what they considered to be idiopathic congenital dilatation of the pulmonary artery. In these individuals, the pulmonary artery was abnormally large by roentgenogram. There was a higher pressure in the right ventricle than in the pulmonary artery, but the right ventricular pressure was not sufficiently elevated to be considered above the range of normal. Because of the normal pressure in the right ventricle and low pressure in the pulmonary artery in the presence of a dilated pulmonary artery, they attributed the pressure difference not to a narrow outlet between right ventricle and pulmonary artery (pulmonic stenosis) but to a pre-existing dilated pulmonary artery. In this instance, "pressure is dissipated as the result of an abnormal deformability of the pulmonary artery and of its main branches due to dilatation and the thinness of the wall and because the flow at the site of the dilatation becomes turbulent. The systolic pressure in the right ventricle obviously should not be increased."

It would appear to us that this conclusion should be considered in greater detail from the hemodynamic standpoint. The possibility is suggested that during exercise the pressure in the right ventricle might rise abruptly without similar rises of pressure in the pulmonary artery as in Cases 2 and 6 of the present study. It is also to be noted that in acquired dilatation of the pulmonary artery in association with atrial septal defect, there is no significant difference in the systolic pressures in the right ventricle and pulmonary artery despite at times enormous dilatation of the vessel and large blood flows through it, both of which should exaggerate the pressure differences over and above those present in simple pulmonic sten-

osis where blood flows are within the normal range. Cases 5, 7, and 8 had right ventricular pressures which were within or practically within the normal range. In view of the above considerations, we believe them to be examples of dilatation of the pulmonary artery secondary to mild pulmonic stenosis rather than of idiopathic congenital dilatation of the vessel. Our criteria for diagnosis of the latter condition would include the absence of any systolic pressure difference between right ventricle and pulmonary artery and the absence of any abnormal elevation of pressure in, or blood flow through the pulmonary artery at rest. To date we have encountered only one such case.

Prognosis: The outlook is related to the degree of stenosis. In none of our cases was the calculated stenosis resistance high, indicating that pulmonary obstruction was of mild degree. All the patients were doing well without restriction. From the literature patients may die in infancy or live a normal life span. Previously, subacute bacterial endocarditis was a major threat. With the advent of antibiotics, this complication is still serious but less so than before. Pollack and associates[5] observed striking improvement in a patient following cure of subacute bacterial endocarditis and postulated that the infection had served to widen the stenotic area. Congestive heart failure is the natural sequel in all but the mildest cases. Surgical intervention has already been undertaken[47] and it would seem reasonable to suppose that as the operative technique becomes perfected, pulmonic stenosis will be another example of curable heart disease.

Diagnosis: The important and almost diagnostic findings in pulmonic stenosis are: (1) a pulmonic systolic murmur as described; (2) a prominent pulmonary artery as demonstrated by x-ray and fluoroscopic studies; (3) normal or decreased pulmonary vascular markings by x-ray examination; and (4) right ventricular hypertrophy by electrocardiogram. The only constant finding is the murmur which by itself is not diagnostic. An enlarged pulmonary artery is not always present and the electrocardiogram may show no ventricular hypertrophy in the presence of mild pulmonic stenosis. It is then difficult, if, indeed, possible to differentiate these cases from simple ventricular septal defect (Roger's disease) or from a small atrial septal defect without resorting to venous catheterization. In our experience, simple ventricular septal defect is rare. In her Atlas, Abbott[19] listed 50 in 1,000 cases of congenital heart disease as opposed to only 9 cases of pure pulmonic stenosis. Keith,[39, 48] on the other hand, seemed to observe pulmonic stenosis relatively frequently, although precise figures are lacking, and simple ventricular septal defect only 9 times in 272 cases. In all but the mildest cases of atrial septal defect, ventricular septal defect, Eisenmenger's complex, pulmonary vascular disease, and patent ductus arteriosus, the pulmonary vascular markings are accentuated. In all of these conditions with the exception of patent ductus arteriosus, the murmur may be identical with that of simple pulmonic stenosis.

The appearance of cyanosis in these individuals may be misleading, the main differential being the tetralogy of Fallot, Eisenmenger's complex, and atrial septal defect with or without associated defects. In the tetralogy of Fallot, cyanosis dates from birth. In atrial septal defect and Eisenmenger's complex, cyanosis usually appears late in the course of the disease, but pulmonary vascular markings are prominent by x-ray examination.

Differentiation of simple pulmonic stenosis from pulmonic stenosis with an associated ventricular septal defect but without overriding of the aorta has been impossible in our experience without the use of venous catheterization. Depending on the relative pressures in the right and left ventricles, the shunt may be from left-to-right (acyanotic) or from right-to-left (cyanotic).[10]

Summary

1. Eight cases of physiologically uncomplicated congenital pulmonic stenosis are reported and discussed in relation to other reported cases.

2. Diagnosis was made by cardiac catheterization with the finding of a significantly higher systolic pressure in the right ventricle than in the pulmonary artery.

3. In none of our cases was the stenosis of

severe degree as indicated by history, calculated degree of stenosis, and circulatory dynamics in response to exercise.

4. Although uncomplicated pulmonic stenosis has always been considered a rare condition, it would appear to be one of the common types of congenital heart disease as indicated by cardiac catheterization.

5. All degrees of mildness and severity of stenosis may occur with resulting short or long life span.

6. Cyanosis and even clubbing of the digits may appear late in the course of the disease, the cyanosis apparently being on the basis of a poor peripheral circulation.

7. Cardiac failure when it does occur is characterized by peripheral chronic passive congestion, the lungs remaining remarkably free of râles and edema.

8. The murmur is systolic in time, is maximal in the second, third or fourth left intercostal space, may be widely transmitted over the precordium and back, but its transmission into the neck is minimal or absent. Its loudness bears little relation to the severity of the stenosis. There is occasionally an associated diastolic murmur of insufficiency. The pulmonic second sound may be normal, diminished, or increased in intensity.

9. Arrhythmias may occur but are not common.

10. The characteristic roentgenologic pattern is enlargement of the pulmonary artery, normal or decreased pulmonary vascular markings, a left auricle and ventricle of normal size, and, if the stenosis is severe or of long standing, enlargement of the right ventricle and auricle.

11. Electrocardiographically, 2 of our 8 patients had right ventricular hypertrophy, 3 had incomplete right bundle branch block, 2 had normal tracings, and 1 had changes suggestive of left ventricular hypertrophy with intraventricular block.

12. Pathologically, pulmonic stenosis may be valvular, may be represented by a fusiform narrowing of the infundibular portion of the right ventricle, or may be a narrowing of the ostium infundibuli between the main (lower) and infundibular (upper) chamber of the right ventricle. By pressure tracings, it seems doubtful if the first two can be distinguished from one another, but Case 2 is thought to be indicative of stenosis of the ostium.

13. Additional findings at autopsy include an enlargement of the right auricle and ventricle, no enlargement of the left auricle and ventricle, dilatation of the pulmonary artery the nature of which has not yet been elucidated despite considerable speculation, and chronic passive congestion of the viscera but not of the lungs.

14. These patients are vulnerable to subacute bacterial endocarditis.

15. The clinical diagnosis depends on roentgenographic and electrocardiographic findings in those with a pulmonic systolic murmur and a compatible clinical course. The differential diagnosis is discussed.

Acknowledgments

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Failure of Alpha Tocopherol to Influence Chest Pain in Patients with Heart Disease

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Claims for vitamin E in angina pectoris have not been based on controlled observations. Even some negative reports have not been adequately controlled as to nonspecific factors. Hence, this study of the effects of alpha tocopherol on cardiac pain used a method of investigation carefully controlled as to psychologic factors which might affect the patient's response or the examiner's interpretation of results. The dose of synthetic alpha tocopherol acetate (300 mg. by mouth daily for two or more months) was the same as that recommended by advocates of this form of therapy as optimum in most cases. The results failed to indicate that the vitamin possessed any advantage over the placebo for treatment of either effort angina or mixed types of cardiac and somatic chest pain.

DURING the course of our studies on the visceral and somatic components of chest pain in patients with heart disease,[1–4] Vogelsang, Shute and Shute[5–9] and Molotchick[10] reported beneficial effects of vitamin E on "anginal pain" and heart disease. It occurred to us that the relief of pain in such cases might be due, at least in part, to effects of vitamin E on the voluntary muscles rather than on the heart. This concept was supported by the fact that animals deprived of vitamin E show reversible changes in both cardiac[11, 12] and skeletal[13, 14] musculature, and by reports on the usefulness of vitamin E in the muscular dystrophies and somatic pain syndromes such as fibromyositis.[15–18]

We decided, therefore, to classify chest pain in our cardiac patients according to visceral and somatic components, and to evaluate by the blind-test method the effect of alpha tocopherol on these components in parallel series of control and treated subjects. The need for such a blind-test study is emphasized by Vogelsang, Shute and Shute themselves,[9] as well as by recent editorial comment.[19] The latter concludes: "Subjective benefits claimed [for vitamin E] may justify a series of well controlled experimental studies in human heart disease to determine whether purely psychologic or real physiologic changes are involved." Unfortunately, neither the initial favorable reports on vitamin E therapy,[5–10] nor later negative results of other investigators[20–21] were based on observations adequately controlled with respect to nonspecific factors.

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The synthetic alpha tocopherol (Ephynal Acetate) and matching placebo tablets were supplied by Hoffmann-La Roche, Inc.

Methods

Forty-one ambulatory patients with chronic chest pain and with arteriosclerotic and/or hypertensive heart disease were selected at random from the Cardiac Clinic. Three patients refused to continue their medication after varying periods of time and are discussed later. Thirty-eight patients completed the course of therapy, 19 having received synthetic alpha tocopherol and 19 a matching placebo tablet.

The study was conducted according to stringent blind-test methods. After preliminary study the patients were paired and matched with respect to sex, age, cardiovascular status, duration and type of chest pain, and other pertinent factors (table 1). One of each pair was allotted by chance to either the control (placebo) or treated (vitamin) group. It may be seen from table 1 that the two groups are closely comparable. None of the examiners knew whether vitamin or placebo was being administered to any particular patient. The physician (S.H.R.) who administered the medication never examined the patients. Even in the analysis of the data the final evaluation of the effect of medication was made in each case without knowledge as to whether the patient was in the treated or control group.

These 38 patients exhibited three types of chest pain: (1) effort angina—pain in any part of the chest regularly induced by walking and promptly relieved by rest and/or nitrites (14 treated, 13 control); (2) constant chest pain—pain present most of the time to a greater or lesser degree (2 treated, 1 control); and (3) intermittent chest pain unlike effort angina

(2 treated, 2 control). We regard the chest pain in the first group as being primarily of cardiac origin and in the latter two groups as being chiefly somatic. Two patients had both effort angina and constant pain (both control). During the preliminary period of observation, two patients with effort angina became free of their chest pain a few days before medication was begun (1 treated, 1 control). We kept these patients in the study in order to note whether pain recurred while on medication; in neither instance, however, was there recurrence of chest pain.

None of the patients had pain on breathing, such as characterizes pleurisy or intercostal neuralgia, nor was the pain traceable to any pulmonary lesion.

To evaluate effects on the somatic factor of cardiac pain, at each visit the presence and location of tender areas in the chest muscles were noted on special charts, together with a description of pain reference induced by pressure on specific trigger areas.[2] Areas of spontaneous pain, whether constant or related to effort, were also mapped. The muscles examined included the sternalis, pectoralis major and minor, serratus anterior, erector spinae (especially the multifidus and iliocostalis), and other scapular and interscapular muscles. These examinations were repeated at each visit, usually every two or three weeks. A total of 365 visits were made by the 41 patients, exclusive of those for laboratory tests.

Initial laboratory work included electrocardiograms, x-ray examinations of the heart and spine, complete blood counts, urinalysis, blood chemistry, and determination of blood sedimentation rates. The electrocardiograms were repeated at intervals during the study, and other tests as indicated.

Special tests included the following:

1. Measurement of the patient's capacity for effort without pain, or exercise tolerance. At intervals of several weeks this test was carried out according to the two-step technic under standard conditions previously described.[25, 26] In 9 patients the results of the test were inconclusive because of indecisive end points. On 13 patients the test could not be performed because pain on effort was not present, or because pain in the joints of the lower extremities prevented walking over steps, or because of intermittent claudication.

2. Measurement of skeletal muscle power. A spring device grip recorder, standardized in arbitrary units, was used to measure the strength of the grip in each hand.

3. Measurement of skeletal muscle endurance. Deep pain was produced by contraction of the forearm muscles during ischemia by a technic similar to that of Lewis,[27] Harrison and Bigelow,[28] and others. The pressure in the cuff was raised to a minimum of 200 mm. Hg, or if the systolic blood pressure was more than 150 mm., to 50 mm. above this. A metronome, set for one beat per second, was used to maintain a constant rate of thirty flexor contractions per minute. On alternate beats, the patients closed and opened the fingers; the two movements were recorded as a unit by a mechanical counter. The patient stopped when there was so much pain that he could no longer keep up with the metronome. The end point was usually quite sharp: sudden inability to move the fingers on account of pain.

The plan of medication was as follows: Alpha tocopherol was given in doses of 200 mg. daily by mouth for two weeks, and then 300 mg. daily. This was administered in divided doses of 100 mg. each.

TABLE 1.—*Initial Status of Treated and Control Groups with Respect to Various Factors*

Factors	Alpha tocopherol (19 cases)	Placebo (19 cases)
	(no. cases)	(no. cases)
Sex: Males	9 (47%)	13 (68%)
Females	10 (53%)	6 (32%)
Age: Average	61 yrs.	59 yrs.
Range	(49–72)	(47–77)
Chest pain		
Duration: Average	6.1 yrs.	7.4 yrs.
Range	($\frac{1}{3}$–15)	($\frac{1}{6}$–15)
Type: Effort angina	15 (79%)	14 (74%)
Somatic pain	4 (22%)	5 (27%)
Cardiovascular		
Hypertension	6 (32%)	8 (42%)
Previous myocardial infarction	9 (47%)	7 (36%)
Abnormal electrocardiogram	8 (42%)	11 (58%)
Congestive heart failure	0 (0%)	0 (0%)
Miscellaneous		
Somatic pain syndromes (exclusive of chest)	12 (63%)	13 (68%)
Osteoarthritis of spine	19 (100%)	19 (100%)
Diabetes mellitus	1 (5%)	2 (11%)
High blood sedimentation rate	2 (11%)	2 (11%)
Anemia	0 (0%)	0 (0%)

A similar number of the matching placebo tablets was prescribed. For the 38 patients in the final series, administration of alpha tocopherol averaged sixteen weeks (ten to twenty weeks), and of the placebo 16.6 weeks (ten to twenty weeks). The 3 patients of the original series who discontinued medication (alpha tocopherol), stopped the drug because of increased chest pain in one, two, and five weeks, respectively. Use of iron salts and mineral oil was prohibited because it has been suggested that these substances might interfere with the absorption of alpha tocopherol.[5, 9, 29] Nitroglycerine and digitalis, if in use, were continued as before.

Results*

Chest Pain. It may be seen from table 2 that the response to medication was essentially the same for alpha tocopherol and for the placebo. Thus, no improvement was noted in 63 per cent of the 19 treated subjects and in 73 per cent of the 19 controls. Subjective improvement was reported by 37 per cent of the treated patients and by 27 per cent of the controls. Two of the control subjects who were classed as unimproved had intercurrent clinical complications—one patient developed congestive heart failure and the other, an acute myocardial infarction. These complications occur naturally in the course of arteriosclerotic heart disease, and in so small a series it cannot be considered statistically significant that both of these patients were in the control group. It may be noted that the only changes observed in the serial electrocardiograms occurred in the patient with the infarction, and these changes were related to this acute episode.

When the effect of medication was analyzed with respect to visceral and somatic components of chest pain, it was found that the results were again similar in the treated and control groups (table 3).

In 2 patients, trigger areas present in the chest muscles on the initial examination disappeared during medication (1 treated, 1 control). Five patients who were without such areas of deep tenderness at the start, remained so. In all other patients, the same tender areas in the

Table 2.—*Response to Medication for All Types of Chest Pain*

Response of chest pain	Alpha tocopherol	Placebo
	(no. cases)	(no. cases)
Total	19	19
No improvement	12 (63%)	14 (73%)
Improvement	7 (37%)	5 (27%)

Table 3.—*Response to Medication According to Type of Chest Pain**

Type of chest pain	Response of chest pain	Alpha tocopherol	Placebo
		(no. cases)	(no. cases)
Effort angina	Total	15	14
	Same	10 (67%)	9 (64%)
	Better	5 (33%)	3 (22%)
	Worse	0 (0%)	2 (14%)
Somatic chest pain (constant and intermittent)	Total	4	5
	Same	2 (50%)	3 (60%)
	Better	2 (50%)	2 (40%)
	Worse	0 (0%)	0 (0%)

* Two patients appear twice in this analysis since they have both effort angina and constant chest pain. The two patients who became free of chest pain just before start of medication are excluded.

Table 4.—*Influence of Medication on Capacity for Work of Cardiac Muscle (Exercise Tolerance Test)*

	Alpha tocopherol (8 cases)	Placebo (8 cases)
Average no. trips before medication	17 (4–25)	23 (4–39)
Net change at end of medication	+6% (−70% to +125%)	+110% (−29% to +633%)

Table 5.—*Analysis of Data in the Seven Patients Who Considered Their Chest Pain Improved by Medication (Alpha Tocopherol)*

Basis of patient's evaluation	Exercise tolerance net change at end of study (%)
Effort angina	
Can now walk 6 or 8 blocks without pain, formerly only 2 blocks	−70
Now walks same distance as before medication, but pain is less severe	−12
Can walk much further without pain: now 46 blocks, formerly only 2½ blocks	+6
Attacks occur less often now than before medication	−5
Can continue walking a little distance after onset of pain whereas before he had to stop at once	+20
Intermittent chest pain	
Attacks now occur at longer intervals; pain just as severe during attacks	Not done, old leg injury
Attacks occur less often and are also less severe	−17

* A preliminary report has been made.[30]

chest muscles persisted throughout the period of observation (15 treated, 16 control).

Satisfactory exercise tolerance tests were obtained on 16 patients (8 treated, 8 controls). Analysis of the results (table 4) reveals an average net increase of 6 per cent in exercise tolerance for the treated group, and 110 per cent for the control group. This average value of 110 per cent includes one patient in the control group who had a very large percentage increase in exercise tolerance (633 per cent). This patient had had an acute myocardial infarction six months prior to the initial exercise tolerance test, and it is likely that the final test five months later reflects spontaneous improvement in myocardial function during recovery from this acute episode.

Seven patients said that they were much better as the result of alpha tocopherol medication (table 5). It should be noted that the improvement is a matter of degree, rather than total relief of pain. The majority of these did not show a corresponding improvement in exercise tolerance. Furthermore, the patients on placebo medication who said they were much better (table 6) made exactly the same kind of statements regarding relief of pain as did those on alpha tocopherol. This indicates the need for parallel series. In fact, one patient expended his supply of the placebo tablets two days before his final visit and stated that his chest pain became much worse in those two days.

TABLE 6.—*Analysis of Data in the Five Patients Who Considered Their Chest Pain Improved by Medication (Placebo)*

Basis of patient's evaluation	Exercise tolerance net change at end of study (%)
Effort angina	
Can now walk 12 blocks without pain, formerly only 2 blocks	+633
Attacks of pain much less severe	0
Can now walk 3 blocks without pain, formerly only 1 block	Test refused
Intermittent chest pain	
Less severe chest pain	Not done, intermittent claudication
Constant and effort angina	
No more constant pain. Pain still occurs on walking as before	+200

Skeletal Muscle. Objective evidence of improvement in this function was also lacking. The measurements of grip, that is, muscle strength, showed a net change after medication of −5 per cent for the treated, and +2 per cent for the control group (table 7). Similarly, with respect to skeletal muscle endurance or capacity for work during ischemia, the net change after medication is similar for the vitamin-treated and the placebo-treated subjects. The increase of 14 per cent and 25 per cent for treated and control groups, respectively, may be due to training.

TABLE 7.—*Influence of Medication on Capacity for Work of Skeletal Muscle*

		Alpha tocopherol (19 cases)	Placebo (19 cases)
Muscle strength (grip)	Average no. units before medication	38 (19–59)	47 (22–62)
	Net change at end of medication	−5% (−40% to +32%)	+2% (−42% to +32%)
Endurance during ischemia (deep pain tolerance)	Average no. contractions before medication	44 (27–92)	44 (20–86)
	Net change at end of medication	+14% (−48% to +96%)	+25% (−36% to +100%)

Hypertension. It has been recommended that doses of only 150 mg. of alpha tocopherol be given initially to patients with hypertension because larger doses raise the blood pressure.[9] Our data show that the blood pressure was not elevated by 200 mg. and 300 mg. doses of alpha tocopherol, even in the 2 patients with systolic blood pressure levels of 210 and 220 mm. Hg respectively. Furthermore, in none of the 6 pa-

tients with hypertensive heart disease who received alpha tocopherol, was there any significant lowering of the blood pressure.

Toxicity. No toxic effects were attributable to these doses of alpha tocopherol. The 3 patients who insisted on discontinuing the vitamin therapy because of increased pain were subject to spontaneous exacerbations of chest pain prior to this medication. Other complaints during vitamin administration were palpitation, spots before the left eye, and sleepiness. On the other hand, 3 patients who received the placebo blamed it for causing nausea, constipation, and weakness, respectively.

Discussion

Evaluation of drug therapy in cardiac pain is fraught with pitfalls due to the many nonspecific factors that may contribute to relief of pain in this condition.[4] It is because of this that we took care to establish a control group as similar as possible to the treated group (table 1), and to conduct the study under doubly blind conditions. Not only were the patients unaware of the nature of the agent being administered, but also those who examined the patients and evaluated the results were ignorant of the material given in any particular case.

As we have indicated, the response to alpha tocopherol was essentially the same as that to the placebo, namely, subjective relief of pain in 37 per cent and 27 per cent, respectively (table 2). These figures are in accord with the observations of Evans and Hoyle[31] that the administration of a placebo to patients with angina pectoris was accompanied by a diminution of pain in 40 per cent of the cases.

Our results fail to confirm those of Shute, Shute, and Vogelsang[6] who reported some degree of improvement in 96 per cent of 84 patients with "anginal pain" on daily doses of about 200 mg. to 300 mg. of alpha tocopherol; 5 of their patients received 400 mg. and one, 600 mg. daily. They regard a dose of 200 mg. as optimum in 80 per cent of cardiac cases.[9] As for the speed of effects, they state[9] "A favorable response to tocopherol therapy may begin at once, but oftener does not appear for 5 to 10 days." They noted that occasionally a therapeutic result may not appear for as long as six weeks. According to these criteria, the periods of about two and one-half to five months, during which our patients received "optimum" doses of alpha tocopherol, represent adequate time for clinical trial.

Failure of alpha tocopherol to relieve angina pectoris has likewise been reported by others. Ravin and Katz[20] gave the equivalent of 250 mg. of alpha tocopherol daily to 11 patients with effort angina for an average of fourteen weeks (four to twenty-four weeks). Levy and Boas[21] administered 200 mg. to 800 mg. of alpha tocopherol daily to a similar group of 8 patients for from three to twelve weeks. Baer, Heine, and Gelfond[22] employed a daily dose of 300 mg. to 400 mg. of vitamin E in 5 such patients. Makinson, Olesky, and Stone[23] gave 150 mg. daily of vitamin E to patients with angina pectoris for three weeks. None of these investigators found unequivocal improvement in cardiac pain. Ball[24] gave 300 mg. of alpha tocopherol daily to 10 such patients for at least six weeks, and observed some diminution of pain in 4, but noted that this effect was comparable to the 40 per cent improvement which follows administration of a placebo to patients with angina pectoris.

Summary and Conclusions

1. Effects of synthetic alpha tocopherol and a placebo were compared by the blind-test method in 41 ambulatory patients with chronic chest pain and heart disease (chiefly arteriosclerotic and hypertensive). Thirty-eight patients completed the course of medication; 19 received the vitamin, and 19 the placebo.

2. Most of the patients (76 per cent) had effort angina alone; the remainder exhibited mixed types of cardiac and somatic chest pain.

3. Synthetic alpha tocopherol was given by mouth in daily doses of 200 mg. for about two weeks, and 300 mg. thereafter. A similar number of matching placebo tablets was given.

4. The average duration of administration of the vitamin was sixteen weeks (ten to twenty weeks) and of the placebo, 16.6 weeks (ten to twenty weeks).

5. No toxic effects of these doses of alpha tocopherol were noted.

6. The effects of medication on chest pain

and on objective measurements of cardiac and skeletal muscle function were similar for the group given alpha tocopherol and for the controls who received the placebo.

7. Our results fail to confirm the reported benefits of alpha tocopherol in cardiac pain.

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Dilatation and Pulsation of the Left Subclavian Artery in the Roentgen-Ray Diagnosis of Coarctation of the Aorta

Roentgenkymographic Studies in Thirteen Cases

By HERBERT M. STAUFFER, M.D., AND LEO G. RIGLER, M.D.

Postero-anterior chest roentgenograms in 17 of 20 patients with coarctation of the aorta showed widening of the left upper mediastinal shadow attributed to dilatation of the left subclavian artery; pulsations of this vessel were evident in 12 of 13 cases with roentgenkymograms. In 3 of the latter cases rib notching was absent or equivocal. The subclavian pulsations may be observed fluoroscopically. Recognition of dilatation and pulsation of the left subclavian artery may provide roentgenologic corroboration of a diagnosis of coarctation of the aorta even in the absence of rib notching.

ENLARGEMENT of the left subclavian artery is a well recognized and almost constant anatomic feature of coarctation of the aorta when the constriction is distal to the origin of that artery. The resultant widening of the left upper mediastinal shadow above the level of the aortic arch has been mentioned occasionally in the literature as a roentgen-ray finding in certain cases.[1, 6, 10, 11] Recently Gladnikoff and his associates[3, 4] have thrown new emphasis on this finding; Gladnikoff states: "The only changes which are pathognomonic are:

"1. Widening of the left subclavian artery, visible as (a) an S-curved outline of the left border of the superior mediastinum, (b) an impression upon the oesophagus, (c) an indentation of the left border of the posterior mediastinum, (d) a modification of the impression of the aortic arch upon the oesophagus.

"2. The discrepancy between the increased pulsations in the left subclavian artery and the decreased pulsations in the adjacent part of the descending aorta."

Laubry and Heim de Balsac[7] had earlier described the diminution of pulsations of the descending aorta as compared with the ascending aorta, recorded in the roentgenkymogram.

Recently the study of patients with coarctation of the aorta at the University of Minnesota Hospitals prior to surgical treatment has provided an opportunity to evaluate these roentgen-ray features in a considerable number of subjects over a relatively short period of time. Our material consists of 20 patients, 13 with roentgenkymograms in the posteroanterior projection; (4 patients from other hospitals are included because their roentgen-ray studies included kymograms). Examination of the roentgenograms in this series of patients provided convincing evidence of the diagnostic importance of the left subclavian artery shadow. Some degree of enlargement of the left upper mediastinal shadow was recognizable in the great majority of the cases. In all but one of the roentgenkymograms, abnormal pulsations of arterial type were distinctly visible on the left above the aortic arch. Marked scoliosis due to old tuberculosis of the spine may well have prevented visualization of the pulsations in the one patient in whom they could not be recognized in the kymogram.

The ages of the patients ranged from 7 to 72 years; a report of the patient aged 72 years appears elsewhere.[5] By decades the patients were distributed as follows:

0–10	1 patient
10–20	6 patients
20–30	7 patients
30–40	3 patients
40–50	2 patients
70–80	1 patient

In 9 of the patients the diagnosis was verified at surgical exploration (in 7 by Dr. Richard L. Varco and in 2 by Dr. Ivan D. Baronofsky). Three further cases not explored were confirmed at autopsy. All cases exhibited the classic clinical findings of coarctation of the aorta.

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Seventeen of the 20 patients showed enlargement of the left upper mediastinal shadow. In almost all instances the shadow was flat, with the border approximately 1 cm. beyond the left margins of the vertebral bodies (fig. 1). The density of the left upper mediastinum was usually noticeably greater than that on the right; vertebral detail was less visible as a result. In only one patient was the arterial dilatation of aneurysmal character; this patient was a man 37 years of age with the clinical findings of coarctation of the aorta, but no rib notching; there was no anatomic confirmation in this case which has been reported briefly elsewhere.[12]

A slight, shallow impression of the left subclavian artery on the esophagus above the aortic arch level was sometimes noted. The aortic impression on the esophagus was regularly minimal and it occasionally appeared to blend with that of the left main bronchus, a point noted by Gladnikoff. The aortic knob was regularly small or unidentifiable; however, in 2 patients, aged 45 and 72 years, respectively, the aortic knob was prominent (fig. 5).

It is our impression that the widening of the vascular shadow above the aortic arch level is very important in rendering the aortic knob inconspicuous in those patients who do not have an associated extensive hypoplasia of the aortic arch (fig. 1).

Several patients showed dilatation of the ascending aorta; this was most pronounced in one patient with well-marked aortic regurgitation, attributed to a probable bicuspid aortic valve (fig. 3).

Twelve of the thirteen roentgenkymograms showed vascular pulsations on the left above the level of the aortic arch. This area normally lacks pulsations (fig. 2). In one patient with evidence of pulsation in the kymogram there was no recognizable left subclavian shadow in the plain film.

It is of greatest interest that in 3 patients showing the pulsating left upper mediastinal shadow there was absent or equivocal evidence of rib notching. In each of these 3 patients the abnormal pulsation was observed fluoroscopically as well. Since 2 of these patients were studied recently, it seems not improbable that such pulsations may have been overlooked during fluoroscopy in earlier cases when we were

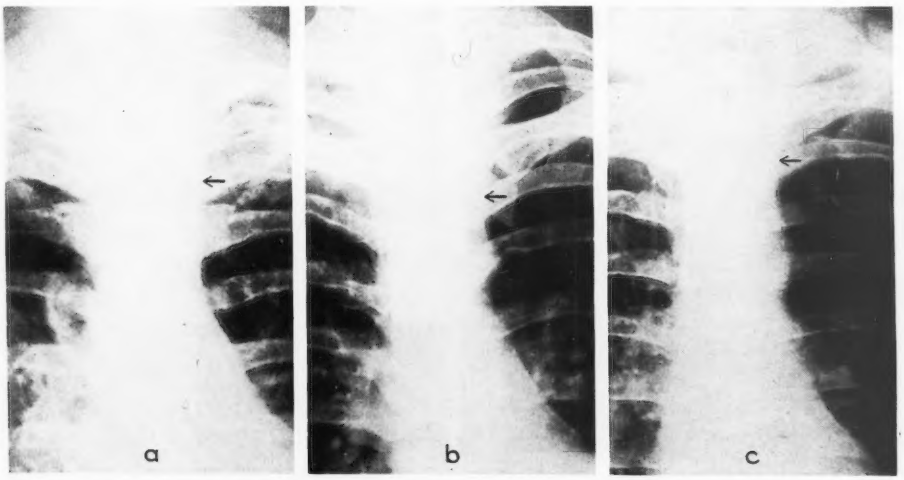

FIG. 1.—Enlarged left subclavian artery shadow (arrows) in 3 patients with coarctation of the aorta. Aortic knob inconspicuous. *a*, The patient was a man 21 years of age. This patient had surgical resection of the coarctation. *b*, The patient was a man 20 years of age. This patient died from subarachnoid hemorrhage. At autopsy, coarctation was found at the usual site with poststenotic dilatation of the aorta; the left subclavian artery was greatly enlarged. *c*, The patient was a man 25 years of age. He had surgical resection of the coarctation.

less aware of its significance; in the third patient there was aneurysmal dilatation of the left subclavian artery.

tion of the aorta involving the origin of the left subclavian artery and patent ductus arteriosus were confirmed on surgical exploration by Dr.

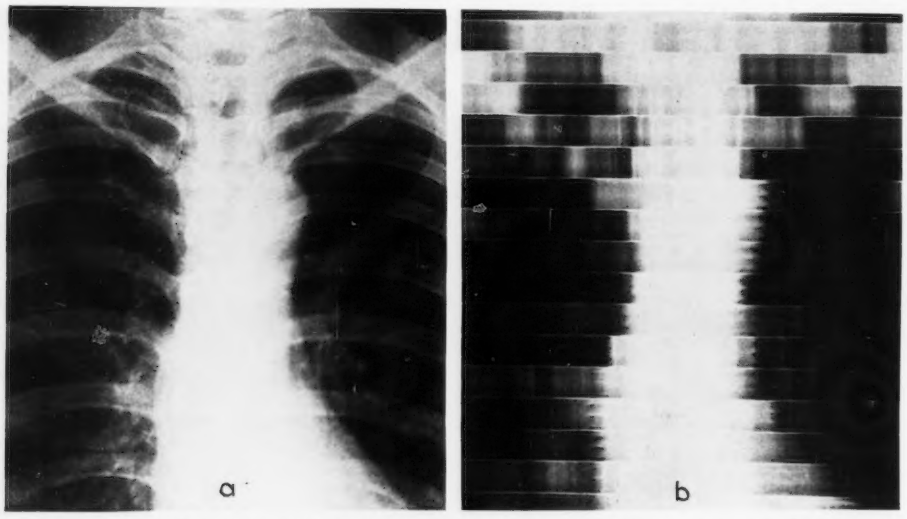

FIG. 2.—Normal appearance of aortic knob and left upper mediastinum in roentgenogram (*a*) and roentgenkymogram (*b*). The patient was a woman 30 years of age. There was absence of pulsations on the left above the aortic knob.

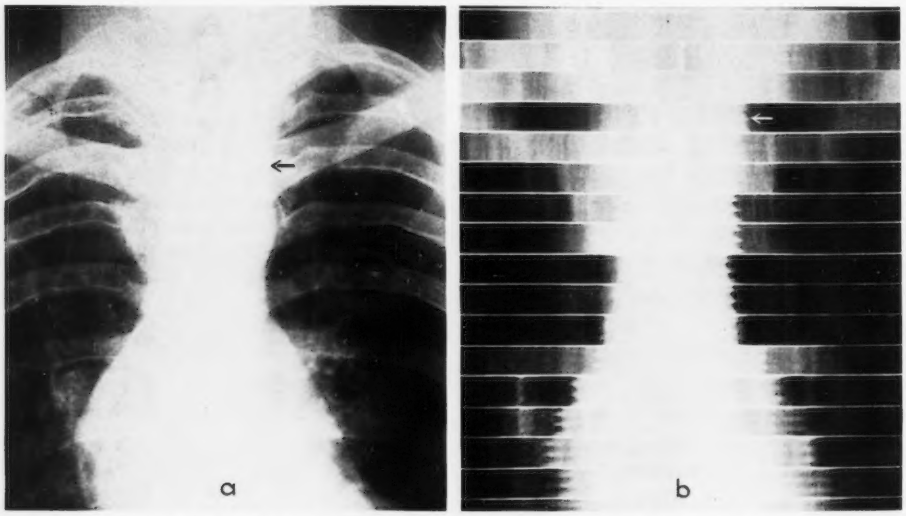

FIG. 3.—Coarctation of the aorta. The patient was a man 20 years of age. He had aortic regurgitation, probable bicuspid aortic valve, dilated ascending aorta, and enlarged, pulsating left subclavian artery.

Figure 4 illustrates one of the cases with supra-aortic pulsations and absence of rib notching; the preoperative diagnoses of coarcta-

Richard L. Varco. Pulsation of the brachiocephalic vessels was the only roentgenray indication of coarctation. The pulsations on the

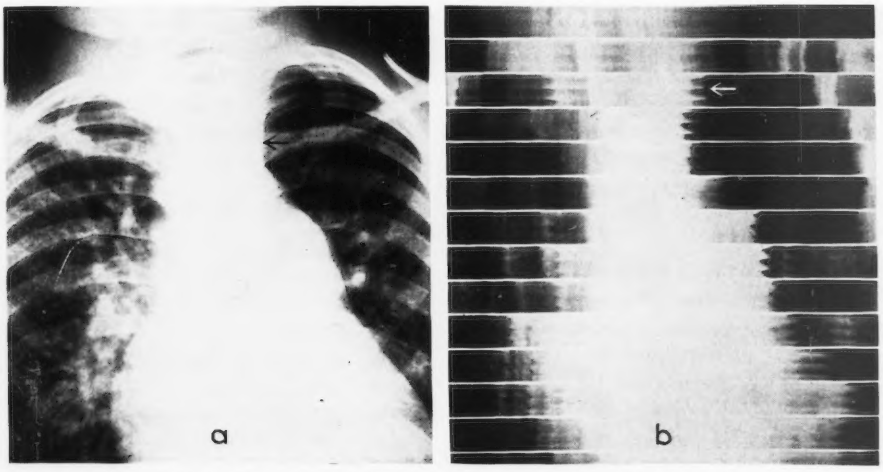

FIG. 4.—Coarctation of the aorta; patent ductus arteriosus. The patient was a boy 7 years of age. There was a widened brachiocephalic vessel shadow (left common carotid) pulsating as shown in kymogram (*b*); the pulsations were obvious fluoroscopically. Clinically there was absence of the left radial pulse and signs of patent ductus and coarctation. Roentgenologically the heart appeared large; the trunk and branches of the pulmonary artery were very large; the aortic arch was small. There was no rib notching. On surgical exploration, coarctation was found beginning proximal to the origin of the left subclavian artery; the left common carotid was greatly enlarged; there was a large patent ductus arising proximal to the coarctation.

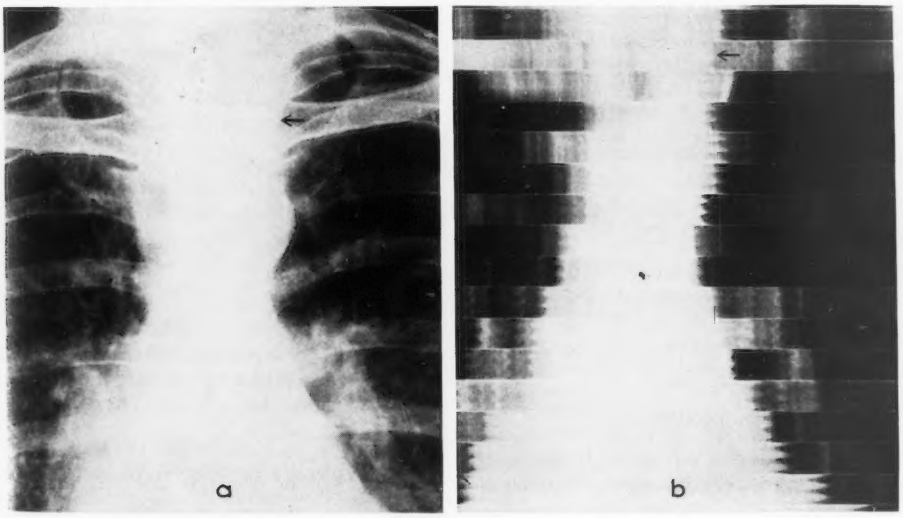

FIG. 5.—Coarctation in a 45 year old man. The aortic knob was prominent owing to ectasia. There was minimal widening of left brachiocephalic vessel shadow (*a*); pulsations were shown in the kymogram (*b*). (Roentgenograms courtesy of Dr. Harold O. Peterson.)

left in this instance were presumably due to the left common carotid since the left radial pulse was unobtainable, the left subclavian arising in the area of coarctation. In the patient reported by Schatzki and Hallerman[10] there was a pulsating mass in the left upper media-

stinum and a pulsus parvus et tardus in the left arm; these authors postulated coarctation proximal to the origin of the left subclavian artery and aneurysmal dilatation of the other brachiocephalic vessels.

In our third patient, a boy of 10 years with equivocal rib-notching, there was pulsation of the left subclavian artery and left ventricular hypertrophy permitting roentgen-ray confirmation of the diagnosis of coarctation; at operation a pin-point lumen at the site of well localized isthmus stenosis of the aorta was found.

The kymographic findings in coarctation with respect to the brachiocephalic vessels are in sharp contrast to those encountered in a review of fifty unselected kymograms of patients with other cardiovascular conditions. Included in this "control" group were examples of conditions with high pulse pressure, such as aortic regurgitation and patent ductus arteriosus; the only instance of pulsation of the left brachiocephalic vessel shadow occurred with aneurysmal dilatation of one of these vessels in a patient with hypertension but no evidence of coarctation of the aorta.

In the kymograms of 2 patients with coarctation, pulsations of the descending aorta were of normal amplitude. In most of the others the outline of the descending aorta could not be made out in the kymogram.

A notch in the dorsal vascular contour near the termination of the aortic arch was visualized in a few of our patients with coarctation in the left anterior oblique view. Study of our cases and of published angiocardiograms[2, 9] indicates that this notch may represent either the site of coarctation or the junction of the dilated left subclavian artery and the aortic arch above the level of the coarctation.

Conclusions

The advent of surgical treatment for coarctation of the aorta makes its early diagnosis of great practical importance. Rib notching, generally accepted as the pathognomonic roentgen-ray sign may occur late and occasionally not at all; minimal indentations of the ribs may be without significance.[8] Dilatation of the left subclavian artery is frequently recognizable in the posteroanterior chest roentgenogram in coarctation of the aorta; regularly in this condition pulsations of this vessel may be recorded in the roentgenkymogram and they may also be recognizable fluoroscopically. Recognition of these signs may provide roentgen-ray evidence for a diagnosis of coarctation of the aorta even in the absence of rib notching.

The widening of the left upper mediastinal shadow by the enlarged left subclavian artery contributes to the characteristic decreased roentgen-ray visibility of the aortic knob in this condition.

In the occasional instances of coarctation of the aorta proximal to the origin of the left subclavian artery, enlargement and pulsations of the left common carotid may be evident roentgenologically. An example of this is included in the present report.

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The Use of Tetraethylammonium Chloride in Treatment of Phantom Limb

By Burton J. Winston, M.D.

The increased number of amputees resulting from World War II has undoubtedly produced many cases of phantom leg symptoms, a condition difficult to manage at best. One is tempted to try every available means to alleviate it, as will be seen in the case reported. In this instance tetraethylammonium chloride proved to be of some value.

MUCH has been written in regard to the treatment of phantom leg symptoms. It is readily conceded that there is no comprehensible explanation for the phantom illusion, yet this does not exclude the fact that there is such a symptom complex. After amputation of an extremity it is usual for the patient to have sensations which seem to originate in the absent limb. In the majority of cases these sensations are most vivid immediately after the amputation, and as time passes they tend to fade from consciousness. The painless variety of phantom limb does not long persist; after a few weeks it tends to melt into the stump and disappear. The painful form lasts longer, and ultimately the surgeon may have to intervene for the relief of these sensations.

The case herein reported was one which proved to be a very serious problem, both to the patient and the physician. The use of tetraethylammonium chloride was decided upon after all other accepted methods of treatment failed.

The report by Berry, Campbell, Lyons, Moe, and Sutler[1] reveals the value of tetraethylammonium chloride compared with lumbar sympathetic block, spinal anesthesia, and local nerve block in patients with vascular diseases and causalgia.

Case Report

I. G., a 77 year old man, was first seen in May 1946 complaining of pain, burning, and cold sensation of his right foot and toes. These symptoms had begun gradually about two years previously, but were becoming progressively worse. He was referred to a physician in Chicago who advised hospitalization for one month with complete bed rest, to be followed by amputation if no relief was obtained.

The patient was admitted to St. Therese Hospital in Waukegan, Illinois, on May 14, 1946. The essential physical findings at that time were as follows: blood pressure 150/90, pipe-stem radial arteries, and tortuous temporal vessels. The patient's feet were cold, there was no dorsalis pedal pulsation, the toenails were hypertrophic, and there was evidence of a beginning gangrenous lesion on the tip of the right little toe. The electrocardiogram showed a right bundle branch block. Hb, 82 per cent; R.B.C., 4,070,000; W.B.C., 6,500 per cu. mm. of blood. The fasting blood sugar value was 87 mg. per 100 cc. of blood. The Kahn reaction was negative. It was quite obvious that this man had an obliterating type of arteriosclerosis. In spite of bed rest, high vitamin diet, vascular exercises and pancreatic extract, he failed to show any evidence of improvement. During this stay in the hospital he required only two hypodermic injections of morphine for the relief of his pain. He refused to have the extremity amputated, and left the hospital on May 22, 1946. However, on June 10, 1946, he was readmitted because the pain was so severe that he readily agreed to amputation, which was performed on June 12. Amputation was done at the level of the junction of the middle and lower third of the right thigh. At the time of operation the nerves were injected with alcohol and were cut several inches shorter than were the muscles and stump. The patient made an uneventful recovery, and was discharged from the hospital on June 22.

On October 14, 1946, he was readmitted to the hospital because of the development of symptoms in the left leg similar to those originally present on the opposite side, with comparable physical findings. The same surgical procedure was followed in performing this left midthigh amputation. The patient left the hospital twelve days following this second amputation. Several weeks after this operation he developed severe burning sensations in his "toes" which seemed equally as painful as before operation. After the appearance of this symptom, numerous hospital admissions followed, during which attempts

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were made to alleviate this most annoying condition. For the purpose of following the chronologic order of the hospital admissions, the dates were as follows: Dec. 13, 1946; April 14, 1947; Aug. 6, 1947. On Oct. 15, 1947, a sympathetic block was performed, followed by little or no relief.

The patient continued to have excruciating pain and choreiform movements of his stumps regardless of therapy. His daughter was shown how to administer the hypodermics and he was given $\frac{1}{4}$ grain of morphine as required to relieve the pain. After several weeks the use of morphine had to be discontinued because of nausea. Pantopon and dilaudid each had their trial and afforded some relief of pain. The patient was becoming addicted to narcotics; he received as many as five and six injections daily. On each of the hospital admissions, an attempt was made to substitute placebos for the narcotic, but it always became necessary to revert to opiates.

At this point, it was decided to try tetraethylammonium chloride (Etamon), since the literature advocated its use in causalgic states. The patient was again admitted to the hospital on November 26, 1947, at 5:30 in the afternoon. A placebo given for relief of pain failed to produce any effect and frequent injections of Dilaudid, grain $\frac{1}{16}$, were required. On November 28, six hours after the last opiate, while he was having excruciating pain, 2 cc. of tetraethylammonium chloride were slowly injected into the right cephalic vein over a period of five minutes. While the drug was being injected the patient stated that he noticed a sensation of warmth in his stumps, along with a complete cessation of pain. His blood pressure prior to receiving the drug was 180/74, and following the injection was 138/68. An electrocardiogram made during and immediately following the injection showed no change. He did, however, complain of a dry metallic taste in his mouth, which disappeared in a few days. On November 29, December 1, and December 6, he was given 6 cc. of Etamon intramuscularly. During the interval between these injections he received several hypodermic injections of sterile water for some slight discomfort in his stumps. Each of these placebos gave relief. We believe that these injections were required to satisfy the addiction phase of his complaints. However, at no time since his initial dose of Etamon was a narcotic required to alleviate pain. He left the hospital on Dec. 8, 1947, free from any discomfort and continued to remain relatively comfortable for a period of nine months without the use of opiates.

In August 1948, he had some recurrence of pain, and again entered the hospital to receive a series of injections of Etamon. He is now free of any symptoms and at the time of this writing he is very comfortable.

Discussion

Autonomic blockade which produces alleviation of pain may do so by means other than by relief of vasospasm alone. It is postulated by Coller and associates[2] that many of the results observed in several series of cases might be explained upon the basis of altered tissue metabolism secondary to sympathetic block. The possibility of a vicious reflex arc being interrupted by ganglionic block with subsequent modification of the pain mechanism must, of course, be given due consideration. According to these authors, if such actually occurs, it still leaves unexplained the duration of relief of symptoms far outlasting the expected duration of the block. It is also possible that certain afferent pathways (if such exist) in the autonomic nervous system may be blocked by the injection of tetraethylammonium chloride and thus contribute to the relief of pain.

Comment

Perhaps some of the results in the case which has been reported may be explained on the basis of the work by Roberts[3] who showed that the vasa nervorum, by being obliterated, may produce an ischemia of an involved nerve segment with resulting pain, numbness, tingling, paresthesia, and other disturbance of the extremity. Karnosh[5] has attributed sciatic causalgia to ischemia of the sciatic nerve. Therefore, we may conclude that the same process that caused the original pathologic state, namely, obliterating arteriosclerosis, was also responsible for occlusion of the vasa nervorum. Thus we can postulate that amputation relieved the peripheral obstruction of the large vessel; it in no way affected the obstructing process in the nutrient vessel to the proximal remaining portion of the sciatic nerve. Since no definite satisfactory explanation for the cause of phantom leg has yet been offered, it is the author's opinion that the neuro-ischemic theory can best explain the causative factors in the greatest number of cases, especially since it has been shown that trauma, sepsis, and vascular diseases are the reasons for the greatest num-

ber of amputations, and are the causes for the involvement of the vasa nervorum. Postmortem examination of the nutrient vessels of the stumps of amputees who had phantom leg symptoms would offer additional information that would prove of great value.

This postulation would conform with the statement of Livingston[4]: "The occurrence and persistence of severe phantom limb pain in a comparatively small proportion of the patients with phantom symptoms, suggests an irritative disturbance that is superimposed on the underlying phantom limb mechanism."

Summary

A case of severe phantom-limb pain is reported. The prolonged and severe pain was resulting in the patient becoming a morphine addict. After all other methods of treatment had failed, the use of tetraethylammonium chloride was attempted and a favorable result was obtained.

An explanation, based on the work of Roberts, is offered for the physiopathologic mechanism which may occur in the production of phantom limb disturbances.

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ABSTRACTS

ARRHYTHMIAS

Murphy, Q., Crumpton, C. W., and Meek, W. J.: The Effect of Blood Pressure Rise on the Production of Cyclopropane-Epinephrine Induced Cardiac Irregularities. Anesthesiology **10**: 416 (July), 1949.

The authors report a further study of a possible role of the pressor effect of epinephrine in the production of ventricular tachycardia by cyclopropane. In these experiments, dogs were tested with minimal pressor doses of epinephrine. Three animals were found in which concentration of epinephrine that produced arterial pressure rises of 6, 6 and 12 mm. resulted in ventricular tachycardia for periods of seventy-five, sixty, and fifteen seconds, respectively. Subsequently, with these animals under the same degree of cyclopropane anesthesia, the aorta was sufficiently compressed to produce a considerably greater rise in blood pressure but there was no change in heart action other than a transient bradycardia.

In a second group of experiments the dose of epinephrine used was larger (0.005 to 0.012 mg. per kilogram). In these experiments the blood pressure rise caused by the injection of the test dose of epinephrine was reduced to a minimum by allowing blood to escape from the animal into a pressure stabilizer. In the first ten experiments, a blood pressure rise is believed to have had little or no important effect on the duration or severity of ventricular irregularities. In three experiments with the same test dose of epinephrine, the irregularities did seem more severe when blood pressure was allowed to rise. In one case the rise in pressure was followed by a brief tachycardia and ventricular fibrillation. In five experiments, ventricular tachycardia did not appear except when blood pressure was allowed to rise.

The authors conclude that there is strong evidence for the belief that a rise in blood pressure is not the cause of the irregularities but that they are in some way due to the action of the epinephrine itself. On the other hand there is evidence that the rise in pressure may influence the appearance of the tachycardia. The threshold for the epinephrine action may have been lowered by the rise in pressure, and thus a dose previously inactive became effective.

BELLET

Long, J. H., Oppenheimer, M. J., Webster, M. R., and Durant, T. M.: The Effect of Intravenous Procaine on the Heart. Anesthesiology **10**: 406 (July), 1949.

The authors describe the effects of rapid injections of 2 or 4 per cent solution of procaine hydrochloride in doses from 4 mg./Kg. to 80 mg./Kg. in 20 dogs. With doses of 4 mg./Kg. there was usually no change in electrocardiogram, heart sounds or blood pressure. Progressive changes occurred as the amount of procaine was increased. Electrocardiographic changes consisted of a heightening, sometimes a flattening or even an inversion of the T wave; lowering of the voltage of R, increase in the depth of the S wave and the formation of a "J" by depression of the S-T segment; increase in the width of the QRS complex; prolongation of the P-R interval; ventricular tachycardia, and, ultimately, ventricular fibrillation. All changes except ventricular fibrillation were reversible, provided that respiration was maintained. When ventricular fibrillation occurred there was no recovery. Blood and pulse pressures dropped as the QRS complex widened, suggesting that there was a loss of tonus and a weakening of the force of the heartbeat in addition to the change in conduction. The greatly dilated heart at necropsy and the flabby condition of the muscle also speak for an effect of procaine on the cardiac musculature.

Small doses (4 to 10 mg./Kg.) caused an increase in respiratory rate which was independent of any change in blood pressure. Larger doses (20 mg./Kg. or more) first increased, then decreased the respiratory rate, suggesting an ultimate depression of the respiratory center. With doses of 40 mg./Kg. or more, respiration usually ceased within thirty seconds of the injection.

The authors conclude that if sudden collapse occurs during the use of procaine, immediate institution of artificial respiration might mean a fair chance of recovery, provided that ventricular fibrillation has not occurred.

BELLET

BACTERIAL ENDOCARDITIS

Traut, E. F., Carter, J. B., Gumbiner, S. H., and Hench, R. N.: Bacterial Endocarditis in the Elderly. Geriatrics **4**: 205 (July–Aug.), 1949.

The authors report that in a series of 13,661 autopsies, 299 or 2.2 per cent revealed active endocarditis. Of the 299 patients, 112 were over and 187 under 45 years of age. In 221 cases the endocarditis

was of the bacterial form (94 of these patients were over 45); in 78, of the verrucous form (18 of these patients were above 45). The 94 cases of bacterial endocarditis in patients over 45 years of age included four times as many men as women. The vegetative or subacute form of bacterial endocarditis was twice as common as the acute or ulcerative type. Almost two-thirds of the cases showed rheumatic scars. Aortic valvulitis predominated in the group with bacterial endocarditis. Mitral valvulitis predominated in the group with active rheumatic endocarditis. Congenital lesions were not important predisposing factors in this series of bacterial endocarditis in the elderly.

BELLET

BLOOD COAGULATION AND ANTICOAGULANTS

Gilbert, N. C., and Nalefski, L. A.: The Effect of Heparin and Dicumarol in Increasing the Coronary Flow Volume. J. Lab. & Clin. Med. **34:** 797 (June), 1949.

The coronary blood flow was determined in dogs under Dial and urethane anesthesia by means of a modified Morawitz-Zahn cannula which was inserted into the coronary sinus. The effect of heparin and dicumarol in altering the coronary blood flow was determined in acute experiments. During the heparin experiments, hirudin was used as an anticoagulant. During the dicumarol experiments, either hirudin or a heparin which was known to have no vasodilator effect was used.

The sodium salt of heparin showed slight to moderate coronary vasodilator effect; the barium salt of heparin did not alter the rate of coronary flow. The authors assume that the vasoconstricting action of the barium ion in the heparin preparation neutralized the dilator effect of heparin. Administration of sodium heparin caused an increase in coronary flow of 77.6 per cent with a fall in blood pressure of 2.7 per cent and an increase in pulse rate of 4.2 per cent.

In the dicumarol experiments the increase in coronary flow amounted to 116.5 per cent, whereas there was no change in pulse rate and there was a drop in blood pressure of 2.9 per cent. Dicumarol also appeared to have a more prolonged action. The solvent used to prepare the sodium salt of dicumarol had no vasodilating effect of itself and was proved to be inert and to have no effect upon rate of coronary flow, pulse or blood pressure. Neither did it alter the anticoagulant effect of the dicumarol. Using the Ostwald technic with blood containing various concentrations of dicumarol and heparin, no change in viscosity could be observed. The sedimentation rate was not altered by heparin or dicumarol. In experiments on the empty beating heart, dicumarol again showed the same effect in increasing the coronary flow as was evident with the heart in situ. Amplitude and force of flow were also increased.

The authors believe that the action of dicumarol is directly on the vessel wall, and that the beneficial results of heparin and dicumarol in coronary thrombosis and angina pectoris are due to the increase in coronary flow which accompany their use.

BELLET

Olwin, J. H.: The One-Stage and Two-Stage Prothrombin Methods in the Control of Dicumarol Therapy, with Remarks on Ac-Globulin. J. Lab. & Clin. Med. **34:** 806 (June), 1949.

The author reports a study of 140 patients on dicumarol therapy for periods varying up to a maximum of two years, with an average of sixty days. In the first 99 cases, the two-stage prothrombin method was used. In 41, the Ac-globulin factor was added according to the modification of Seegers. In 95 cases the one-stage test described by Quick was run either parallel to the two-stage test or at frequent intervals.

In all cases the two-stage method with or without Ac-globulin added gave more uniform readings and provided for a more accurate maintenance of the prothrombin level. The one-stage method in some instances gave results parallel to and usually higher than those of the two-stage test, but in most cases it varied widely from day to day. In nearly all instances the prothrombin estimate according to the unmodified two-stage method was 10 to 20 per cent lower than that of the modified two-stage procedure. In the first week of therapy, however, this relationship may be altered and the one-stage give a lower figure than the two-stage.

The author found that the two-stage method made possible the maintenance of a patient within a desired prothrombin bracket, while the one-stage method on whole or diluted plasma has shown wide variations by comparison. He believes that variation in factors other than prothrombin is often responsible for the one-stage result, but that this test is of value as a summation of various clotting factors. In instances where the two-stage reading is below 10 per cent of normal and the one-stage result is above 10 per cent, bleeding is not likely to develop.

BELLET

Alexander, B., and de Vries, A.: A Factor in Serum which Accelerates the Conversion of Prothrombin to Thrombin: III. Its Relationship to the Coagulation Defect of Thrombocytopenic Blood. Blood **4:** 747 (June), 1949.

Ten subjects with thrombocytopenic purpura due to various causes were studied by the authors. All had platelet counts under 100,000 per cubic millimeter. In each case, the serum prothrombin conversion accelerator (SPCA) was low and the residual serum prothrombin activity was higher

than normal. There was no strict correlation between the bleeding time or platelet count on the one hand and the SPCA or residual serum prothrombin activity on the other, but those subjects with the highest platelet counts seemed to have the highest SPCA activity. The addition of normal oxalated plasma, platelets, or thromboplastin extract to shed thrombocytopenic blood accelerated coagulation, increased prothrombin consumption, and increased the amount of SPCA evolved. In one case of idiopathic thrombocytopenic purpura, there was practically no change in SPCA after splenectomy despite the return of bleeding time and platelet count to normal. Residual serum prothrombin decreased somewhat, but, as the patient relapsed about one month after operation, it again increased.

BEIZER

Alexander, B., de Vries, A., and Goldstein, R.: A Factor in Serum which Accelerates the Converson of Prothrombin to Thrombin: II. Its Evolution with Special Reference to the Influence of Conditions which Affect Blood Coagulation. Blood **4**: 739 (June), 1949.

This paper presents data concerning the evaluation of serum prothrombin conversion accelerator (SPCA) in human subjects under certain conditions which affect blood coagulation. The authors found that immediately after coagulation, SPCA was low, whereas serum prothrombin was high. Within fifteen minutes, SPCA increased to a degree concomitant with a decrease in serum prothrombin activity. During the next forty-five minutes, some prothrombin activity tended to reappear in the serum, and SPCA activity tended to decrease somewhat.

No correlation was seen between the amount of SPCA and the serum prothrombin activity, or the difference in prothrombin activity of the plasmas and their respective sera. There was no apparent relation between the clotting time in glass and SPCA or serum prothrombin activity.

Agitating freshly drawn blood accelerated coagulation. It also accelerated SPCA evolution, increased the amount of it evolved, and decreased the amount of prothrombin activity remaining in the serum. Similar results were obtained by accelerating coagulation by the addition of thromboplastin supplements.

When the coagulation was retarded by handling the blood in siliconized apparatus, the serum showed abnormally high prothrombin activity and small amounts of SPCA. Moderate amounts of heparin added to blood retarded coagulation without affecting either the amount of SPCA evolved or the amount of prothrombin consumed during coagulation. If anything, prothrombin consumption was increased, probably as a result of the greater interval provided by the retarded coagulation for the reaction to proceed. Moderate amounts of heparin seemed to enhance the formation of thrombin. Larger amounts of heparin retarded coagulation by inhibiting the evolution of thromboplastin from platelets or by otherwise preventing the conversion of prothrombin to thrombin. Concomitant with this, SPCA evolution fell off. Serum added to whole blood accelerated coagulation, but the serum expressed from this mixture did not show greater SPCA than the serum from blood allowed to clot alone.

In patients receiving dicumarol, the administration and withdrawal of the drug affected plasma prothrombin concentration and SPCA activity in the same direction: subnormal amounts of SPCA were evolved during the coagulation of hypoprothrombinemic blood.

BEIZER

McLain, P. L. and Ruhe, C. H. W.: The Effect of Various Anticoagulants on the Specific Gravity of Blood and of Plasma, and on the Hematocrit. Blood **4**: 863 (July), 1949.

In this article, the authors further evaluate the changes produced in the specific gravity of blood, serum, and plasma by defibrination and by the addition of heparin, oxalate or citrate. Comparisons are also made of the relative red cell volumes determined by the hematocrit. In the study on which the paper is based the blood used was freshly drawn arterial blood from rabbits.

The specific gravity of whole blood was not significantly altered by defibrination or by the use of the ammonium-potassium oxalate mixture. The specific gravity of plasma was satisfactorily preserved by the use of heparin solution. There was no significant difference between the specific gravity of plasma and the serum obtained from defibrinated blood.

The relative volume of red cells determined by the hematocrit was unaltered by the use of dry heparin, oxalate mixture, 1.6 per cent solution of potassium oxalate, or by defibrination. Dry potassium oxalate and sodium citrate caused marked changes, increasing the specific gravity of blood and of plasma and shrinking the red cells. Dry heparin increased the specific gravity of blood and of plasma. The ammonium-potassium oxalate mixture increased the specific gravity of plasma markedly and consistently.

BEIZER

Holden, W. D., Cole, J. W., and Davis, Jr., J. H.: Clinical Studies of the Heparin Cofactor. Surg., Gynec. & Obst. **89**: 20 (July), 1949.

This study was undertaken to determine whether operative procedures altered the thrombin-inactivating substances of the blood and whether any such alteration could be related to the development of venous thrombosis. The heparin cofactor is designated throughout this paper as the substance in the circulating blood which develops strong anti-

thrombin capacity when heparin is added to it. The heparin cofactor has been designated by a variety of terms such as thrombin co-inhibitor, albumin X, proantithrombin and heparin complement. Its composition is unknown. It is known, however, to be intimately associated with the blood proteins. More specifically, it is more closely associated with the serum albumin.

Heparin cofactor assays were performed on 67 normal fasting individuals. The significant observations were that there was very little alteration in the cofactor activity of the serum when no thromboembolic complications occurred. On the other hand, in 2 patients, when they did occur, there were appreciable reductions in the cofactor activity. Whether the latter is cause or effect remains to be demonstrated. The observation that hypoalbuminemic patients have a consistently reduced cofactor activity verifies the association of the blood albumin and the thrombin inactivating agents. It also suggests one additional reason for correcting a hypoproteinemic state before surgery.

BECK

Fowler, N. O.: A Study of Certain Aspects of Blood Coagulation in the Postoperative State, in Congestive Heart Failure and in Thrombophlebitis. J. Clin. Investigation **28:** 671 (July), 1949.

The coagulation of the blood may be studied by a variety of tests: the silicone tube, the lusteroid tube coagulation tests, clot retraction, Lee-White clotting test, heparin retarded coagulation test of Waugh and Ruddick, the heparin tolerance test, and the prothrombin time. These tests were performed on 29 postoperative patients, 27 with congestive heart failure and 3 with acute thrombophlebitis.

The correlation among the tests was poor, suggesting that they are concerned with different factors in the clotting process. Of the various tests, the Waugh-Ruddick heparin test seemed the most sensitive. By this method, 19 of 29 postoperative patients showed accelerated coagulation. Hypercoagulability at times persisted as long as twelve days postoperatively. However, the tests were of no value in predicting or diagnosing thrombophlebitis. Among the 27 patients with congestive heart failure, 25 of whom were receiving digitalis, only one showed accelerated coagulation in lusteroid tubes and two by the Lee-White test. The clotting time was 4 times longer in a blood sample taken from a vein which had recently received heparin than from a vein of the opposite arm.

WAIFE

BLOOD VESSELS AND VASCULAR DISEASE

Uhlbach, P.: On the Etiology of Spontaneous Rupture of the Aorta. Ztschr. f. Kreislaufforsch. **38:** 283 (May), 1949.

During heavy work a 38 year old man suddenly experienced a severe pain in the chest, particularly on deep breathing. There were no complaints during bed rest of fourteen days' duration but afterward the pain reappeared on walking. Later, continuous pain and dyspnea led to hospitalization. An enlarged heart with a systolic and diastolic murmur over the aorta and a blood pressure of 130/5 was found. The patient died after three months with increasing dyspnea.

Autopsy revealed a heart weighing 710 Gm. and three ruptures of the aorta. One horizontal rupture was found 2.5 cm. above the aortic valves; it measured 10 cm. and involved the inner and middle layers of the aorta. Two more similar longitudinal ruptures of the inner and middle layers were found in the abdominal aorta. In the area of two of the ruptures, bulging of the wall of the aorta was found. Histologic examination revealed disappearance of the elastic fibers, reaching in the first rupture up to the adventitia. It is assumed that the two ruptures in the abdominal aorta did not cause clinical symptoms. No mucoid degeneration and no muscular necroses were found. According to the author, the disappearance of elastic fibers and not a medionecrosis was responsible for the multiple ruptures of the aorta.

SCHERF

Hayes, D. W., Wakim, K. G., Horton, B. T., and Peters, G. A.: The Effects of Dihydroergocornine on the Circulation in the Extremities of Man. J. Clin. Investigation **28:** 615 (July), 1949.

Dihydroergocornine (DHO-180), an alkaloid derived from ergot, was administered intravenously to 20 subjects. The peripheral blood flow was determined by the venous occlusion plethysmograph with a compensating spirometer recorder.

There was an increase in peripheral blood flow which varied with the method of injection and the extremities studied. An average increase of 117 per cent (range 35 per cent to 214 per cent) was noted in the arms of 6 persons when dihyroergocornine was given by infusion. The average increase was 78 per cent in the lower extremities. When the drug was given by a single intravenous injection, the average increase in blood flow was 84 per cent and 63 per cent for the upper and lower extremities, respectively. The over-all average increase for the entire group was 94 per cent in the upper and 68 per cent in the lower limbs. No significant changes in blood pressure were found in normotensive subjects but the pressure did fall in 2 hypertensive patients. A moderate reduction in heart rate was found. Side reactions were observed in all but one case. Nasal congestion producing severe obstructions of the passages was the most common complaint. Nausea, headaches and flushing were also noted.

WAIFE

Diefenbach, W. C. L.: Fatal Jarish-Herxheimer Reaction with Sudden Aneurysmal Dilatation and Complete Bronchial Occlusion Following Penicillin Therapy. New England J. Med. **241:** 95 (July 21), 1949.

A 75 year old man with syphilitic aortitis and aneurysmal dilatation of the aorta was admitted to the hospital with signs of pneumonia. The patient was given 100,000 units of aqueous penicillin every three hours. On the following morning his temperature was normal. On the third hospital day he complained of dyspnea and the trachea was found to be deviated to the left with absent breath sounds anteriorly and posteriorly on the left side. The clinical impression was that the patient had a syphilitic aneurysm and that after penicillin therapy of pneumonia a Jarish-Herxheimer reaction had occurred, with sudden dilatation of the aorta and complete occlusion of the left main bronchus and massive collapse of the left lung. The patient's condition grew worse; death occurred on the fifty-eighth hospital day. Autopsy showed a large saccular aneurysm of the arch and descending aorta occluding the left main bronchus and compressing the lower 4 or 5 cm. of the trachea.

The author suggests that caution be exercised in the penicillin treatment of elderly syphilitic patients for conditions other than syphilis.

BELLET

Morrison, L. M.: Effect of Choline on the Prevention of Experimental Atherosclerosis. Geriatrics **4:** 236 (July–Aug.), 1949.

The author reports the results obtained in the production of atherosclerosis in rabbits by the feeding of cholesterol and the attempt made to prevent this cholesterol-induced atherosclerosis in rabbits by the simultaneous feeding with choline. In Group A, the control group, which was fed 0.5 Gm. cholesterol daily, all animals but one developed atherosclerosis in ninety-two days. In Group B, in which the animals were fed 0.5 Gm. cholesterol daily together with 0.5 Gm. choline chloride, 45 per cent developed atherosclerosis and 55 per cent were free of atherosclerosis in ninety-two days. In Group C, in which the animals were fed 0.5 Gm. cholesterol daily together with 1.0 Gm. choline chloride, 22 per cent developed atherosclerosis and 78 per cent were free of atherosclerosis in ninety-two days.

BELLET

CEREBRAL ARTERIES AND CEREBRAL ARTERY DISEASE

Tennent, E. C. and Harman, J. W.: A Study of Factors Affecting the Prognosis of Cerebral Vascular Accident. Am. J. M. Sc. **218:** 361 (Oct.), 1949.

The correlation of clinical data concerning age, sex, blood pressure and physical signs has been made on 75 cases of cerebral hemorrhage, 27 of thrombosis and 5 of embolism. Of these, 64.5 per cent were followed up successfully. In the assessment of immediate prognosis, the type of accident is important, since 30 per cent of hemorrhages and 7.5 per cent of thromboses are fatal in the first attack. Mortality varies with age, being greatest at the extremes of life, and least in the fifth and sixth decades. In thrombotic accidents, however, age is of relatively slight significance. Brevity or absence of coma indicate a more favorable prognosis, whereas coma lasting longer than forty-eight hours is an ominous sign. The occurrence of atypical respiration, particularly if prolonged or of Cheyne-Stokes variety, is also a sign of considerable gravity. A very high blood pressure (systolic over 190, diastolic over 140) suggests a poor prognosis. The height of the blood pressure is an indicative, not a conclusive sign. It is further suggested that the intermittent distending force of an elevated systolic pressure plays a greater role than the continuous stress due to the maintained diastolic level. Of the survivors of hemorrhage, about 18 per cent have one or more recurrences; 5.6 per cent of these die in the second attack and 11 per cent of the combined subsequent attacks. Unless seriously compromised by the sequelae of the disease, the remaining survivors seem to live out their expected span of life.

DURANT

CONGENITAL ANOMALIES

Callebaut, C., Denolin, H., and Lequime, J.: Oxymetry in Congenital Heart Disease. Acta Cardiol. **4:** 324 (Fasc. III), 1949.

The oxymetric method shows a marked decrease in oxygen saturation of the arterial blood during exercise tests in cases of heart disease with veno-arterial (right to left) shunts. The greater the shunt, the greater the decrease in oxygen saturation. This decrease in oxygen saturation is not found in normal patients, in patients with isolated pulmonary stenosis, or in patients with arterio-venous shunts (for example, pure interventricular defect or patent ductus arteriosus).

The influence of the body position on the oxygen saturation of arterial blood has been studied in patients with congenital cyanotic heart disease. There generally is a higher oxygen saturation when the patients are supine or squatting than when they are standing. This explains certain preferential positions such as squatting. According to the authors, the change in oxygen saturation seems to be due to modifications in the degree of the veno-arterial (right to left) shunt which varies with different positions of the patient.

LUISADA

Barret, N. R., and Daley, R.: A Method of Increasing the Lung Blood Supply in Cyanotic Congenital Heart Disease. Brit M. J. **4607:** 699 (Apr. 23), 1949.

The authors describe an ancillary method of in-

creasing the pulmonary blood supply in patients suffering from forms of congenital cyanotic heart disease in which the main defect is inadequate blood flow to the lungs. It has been found that anastomosis or valvulotomy may not be practicable or advisable in every case. The authors suggest that a simple alternative method might be the production of vascular pleural adhesions which will bring blood into the lungs from the parietes. This method includes opening both pleural cavities at separate operations and removing the parietal pleura from the upper mediastinum, from the dome of the pleura, and from the upper half of the chest. Powdered asbestos is then dusted on to the raw surfaces, the chest is closed, and, after instituting temporary drainage, the lung is completely re-expanded.

Judged by clinical studies, such as improved exercise tolerance, diminution of cyanosis, and less frequent squatting, the authors observed good results in two patients and considerable improvement in 3 patients. Of 4 patients in whom there were details of resting arterial oxygen saturation before and after operation, significant improvement occurred in 3 and no change in one case. In 6 patients the blood oxygen capacity was measured before and after operation and was significantly decreased in 4. One patient, although clinically improved, showed no change in arterial oxygen saturation or oxygen capacity, but his oxygen intake and carbon dioxide production, measured as a percentage of ventilation, changed from markedly abnormal to normal figures. The results may indicate still further improvement after a longer follow-up period than three to four months, but it is thought that as preliminary observations they are encouraging enough to warwant further application of the procedure to patients who for various reasons are unsuitable for the types of surgery already devised.

BELLET

Mossberger, J. I.: Anoxia of the Central Nervous System and Congenital Heart Disease. Am. J. Dis. Child. **78:** 28 (July), 1949.

Accumulated evidence leads to the belief that the central nervous system bears the brunt of any disturbance in gaseous exchange, regardless of its type or cause.

Three cases of uncomplicated cerebral hypoxia accompanying congenital heart disease which came to necropsy are presented. These cases showed neuronal degeneration and necrosis in various degrees of severity and extent, glial reactions ranging from disappearance to hyperplasia, and vascular changes varying from dilatation to proliferation.

In the first patient, a 3 year old white girl with a patent ductus arteriosus and an anomalous subclavian artery, massive postoperative hemothorax produced sufficient cerebral hypoxia, both from loss of blood and collapse of the lung, to cause paralysis of cardiac and respiratory mechanisms. Although these functions resumed after emergency measures, lack of oxygen was either too severe or too long for cellular activity to continue permanently.

The second case was a white male infant born with cyanosis. All supportive measures failed, and the child died forty-six hours after delivery. Retrograde circulation of blood from the left auricle through the foramen ovale, thence to the small aortic arch via the right auricle and ventricle, pulmonary artery, and ductus arteriosus, provided sufficient cerebral oxygenation to sustain postuterine life for two days only.

The third case was a 5 month old male infant with intense cyanosis, caused by transposition of the arterial trunks, a defect in the membranous portion of the interventricular septum, and coarctation of the aorta. As a result of these defects, the upper part of the child's body was in a constant state of oxygen want.

The author draws attention to the natal period and to the importance of maternal anesthesia and infantile apnea as factors which, if not judiciously controlled, may rapidly produce irreversible changes in the child's central nervous system, with consequent neurologic symptoms and impairment of mentality.

BELLET

Direct Inspection of Coarctation of Aorta with a Thoracoscope. Brit. Med. J. **4622:** 317 (Aug. 6), 1949.

A case is described in which there was a chance combination of two diseases: coarctation of the aorta and pulmonary tuberculosis. After a period of bed-rest, a left artificial pneumothorax was induced. In the absence of evidence of gross chest-wall anastomoses thoracoscopy was considered to be a justifiable procedure. During this procedure the aorta was examined both above the upper lobe and through the interlobar fissure. In this way the whole length from arch to coarctation was seen. The notch was easily visible at the posterior end of the fissure. It was a short constriction and well below the origin of the left subclavian artery. Convalescence from thoracoscopy was not complicated by intrapleural hemorrhage.

The authors suggest that thoracoscopy is important since a view of the actual lesion is more informative than any radiologic technic. The risk entailed is hemorrhage from the anastomotic vessels in the chest wall.

BELLET

Kneidel, J. H.: A Case of Aneurysm of the Ductus Arteriosus with Postmortem Roentgenologic Study after Installation of Barium Paste. Am. J. Roentgenol. **62:** 223 (Aug.), 1949.

The author describes a case of aneurysm of the ductus arteriosus in a premature Negro female infant which was diagnosed at autopsy; death occurred

twenty-one days after birth. Only 30 other such cases have been reported and only 6 of the reported cases have occurred in adults, (of whom the average age was 31 years). The remainder have been found in infants less than 2 months of age.

The etiology of aneurysms in this location is probably related to the normal lack of elastic tissue and the abundance of smooth muscle in the ductus, plus the high pressure of blood in the aorta. The peculiar location of such a tumor is its most significant feature. In the posteroanterior and anteroposterior projections, the aneurysm appears to the left and slightly above the pulmonary conus. In the right anterior oblique projection, it lies to the left and superior to the pulmonary conus between that structure and the aortic arch. In the left anterior oblique projection, the clear shadow of the "aortic window" is obliterated by the shadow of the aneurysm.

The author believes that angiocardiography, using the technic of Robb and Steinberg, should establish the diagnosis.

ZION

CONGESTIVE HEART FAILURE

Richards, D. W., Jr.: Dynamics of Congestive Heart Failure. Am. J. Med. **6**: 772 (June), 1949.

Inadequate ventricular emptying during systole is of basic importance in congestive heart failure. Increased ventricular dilatation early in failure probably results in an increased systolic output. Even an increased ventricular diastolic pressure requiring increased venous pressure may be a favorable compensatory factor and result in a maintenance of cardiac output, as in some cases of anemia. Such compensation becomes excessive with eventual overdilatation, decreased stroke volume, and decreasing cardiac output.

In left ventricular failure it is probable that pulmonary congestion is due to inadequate emptying of the left ventricle accompanied by adequate output by the right ventricle.

In accordance with the forward failure hypothesis, right-sided congestion develops secondary to increased blood volume in those forms of failure in which salt and water retention occur early. In those cases in which increased diastolic and venous pressures are secondary to a primarily inadequate right ventricular emptying, the congestion appears before the hypervolemia. Another group of cases shows a low cardiac output with no increase in venous pressure or general congestion. Anything that can be done to prevent the accumulation of blood in venous reservoirs under high pressure is advantageous to tissues and circulation in most instances.

SCHWARTZ

Pugh, L. G. C., and Wyndham, C. L.: The Circulatory Effects of Mercurial Diuretics in Congestive Heart Failure. Clin. Sc. **8**: 11 (July), 1949.

The effects of intravenous injections of mercurial diuretics on right atrial pressure, cardiac output, heart rate and blood pressure were determined in 1[illegible] patients with congestive failure due to rheumatic, hypertensive, and ischemic heart disease. The cardiac catheterization technic was used and the studies were made hourly.

With theophylline-containing compounds there was a rapid fall in atrial pressure and a rise in cardiac output coming on in ten to twenty minutes and wearing off within one hour. This effect was not observed with mercurial diuretics not containing theophylline. With mercurials, all cases showed a gradual fall in right atrial pressure and, in all but 2, a slow rise in cardiac output. This began about two hours after the injection and reached a maximum in five to seven hours. The highest level of cardiac output coincided in time with the lowest level in atrial pressure. As the diuresis subsided, the right atrial pressure showed a slight rise. The cardiac output, however, tended to return to the initial level as the diuresis wore off. No significant change in pulse rate or blood pressure was found. The maximum diuresis was reached on the average about four and one-half hours after the injection.

These circulatory effects of the mercurial diuretics are comparable with those which develop when the right atrial pressure is reduced by venesection or by blood pressure cuffs applied to the thighs. This suggests that the rise in cardiac output is explained by the reduced atrial pressure.

WAIFE

Cates, J. E.: Edema and Potassium Loss in Combined Sodium p-Amino-Hippurate and Penicillin Therapy. Clin. Sc. **8**: 53 (July), 1949.

A 63 year old man with subacute bacterial endocarditis due to an extremely penicillin-resistant strain of *Streptococcus viridans* was given daily ten million units of penicillin together with large doses of sodium *p*-amino-hippurate which delays the renal excretion of penicillin. He promptly became edematous and cyanotic and developed profound muscular weakness. Certain metabolic studies were performed during and after recovery from this effect.

At first, about 240 Gm. of a 12 per cent solution of NaPAH was given by infusion. Later the amount was reduced. According to Cates, this large amount of sodium (25.5 Gm. or the equivalent of 65 Gm. of salt) could explain the edema but not the fall in serum potassium which fell as low as 9.2 mg. and ranged between 10 and 12 mg. per 100 ml. The electrocardiogram revealed depression of T waves in Leads II and III before the serum potassium fell; this persisted until potassium chloride was given.

Calculations of extracellular volume indicate that sodium entered the cells. Potassium was lost in amount greater than could be attributed to destruction of body protein and loss from extracellular

fluid. The danger of inducing sodium retention includes the development of hypopotassemia by replacement of potassium by sodium in the cell.

WAIFE

Threefoot, S. A., Ray, C. T., Burch, G. E., Gronvich, J. A., Milnor, J. P., Overman, W., and Gordon, M.: Concentration-Time Course in the Plasma of Man of Radiomercury Introduced as a Mercurial Diuretic. J. Clin. Investigation **28:** 661 (July), 1949.

A mercurial diuretic labeled with radioactive mercury was injected intravenously into 15 human subjects. Analyses of the concentration of radiomercury in the plasma were then made. It was found that there were three factors affecting the regression curves. The first was the rate of mechanical mixing; the second was the rate of diffusion into tissue spaces and cells and the third was the rate of excretion. The rapid rate of mercury excretion was responsible for the differences in the radiomercury curve as compared to the radiosodium regression curve.

WAIFE

MacKay, E. M., and Pecka, E. F., Jr.: Studies on Experimental Pulmonary Edema. I. Pulmonary Edema From L-Epinephrine and L-Nor-Epinephrine (Arterenol). Proc. Soc. Exper. Biol. & Med. **71:** 669 (Aug.), 1949.

One group of 6 guinea pigs was given l-epinephrine and the other group l-nor-epinephrine. These drugs were administered as hydrochlorides in 0.9 per cent NaCl in concentrations near 0.1 per cent. The solutions were injected into the penile vein in males and intracardially in females. The degree of pulmonary edema was determined by the weight of the lungs.

The results showed clearly that a lesser degree of pulmonary edema is produced by toxic doses of l-nor-epinephrine than by smaller but toxic doses of l-epinephrine. The adrenergic blocking agent, N-(9-fluorenyl) - N - ethyl - B - Chlor - ethylamine - HCl ("SKF-505") prevented the development of pulmonary edema when toxic doses of either l-epinephrine or l-nor-epinephrine were given.

MINTZ

Feinberg, A. R., Isaacs, J. H., and Boikan, W. S.: Clinical Report on the Toxicity of a New Mercurial Diuretic (Thiomerin) for Subcutaneous Administration. Am. J. M. Sc. **218:** 298 (Sept.), 1949.

The new mercurial diuretic, Thiomerin, was administered subcutaneously 2,069 times to 409 patients. Generalized toxic reactions were absent except for occasional development of muscle cramps, fatigue and weakness resulting from too rapid depletion of electrolyte and water. These symptoms were usually corrected by adjusting the frequency of administration and dose, and adjusting the intake of water and electrolyte. No febrile reactions, hypersensitivity states, gastrointestinal symptoms, or systemic reactions were observed. Local, immediate and delayed irritative reactions occurred, but they were minimal. At no time was it necessary to discontinue the administration of Thiomerin because of local discomfort or irritation. No evidence of kidney damage was observed.

The following advantages are attributed by the authors to Thiomerin: (a) There is no apparent systemic toxicity. (b) It is practically painless when given subcutaneously. (c) It is equally or more effective than other mercurial diuretics. (d) Self administration by a patient under a physician's direction is possible.

DURANT

CORONARY ARTERIES AND CORONARY ARTERY DISEASE

Littman, B.: Infarcation of the Interventricular Septum. New England J. Med. **241:** 89 (July 21), 1949.

In a group of 100 cases of coronary artery disease, 25 patients died and 20 of these were examined post mortem. Of these 20 patients with myocardial infarction on whom autopsies were performed, extensive infarction of the interventricular septum with considerable coincident involvement of the anterior or posterior walls of the left ventricle or both was observed in 11.

The data obtained in the 11 cases indicates that the most frequent electrocardiographic pattern in addition to patterns of specific infarction is that of impaired interventricular conduction or frank bundle-branch block. The Roesler and Dressler pattern was observed less commonly (when both anterior and posterior myocardial walls were involved, together with the septum) and still less frequently was the picture of uncomplicated myocardial infarction seen. In this series the pattern of simple infarction was always that of the posterior wall. Patients who anatomically had extensive involvement of the anterior wall together with septal disease invariably showed bundle-branch block. The author states that mortality with extensive infarction of the interventricular septum is about 70 per cent.

BELLET

MacDougall, W. G.: Fatal Coronary Occlusion in a Girl Aged 16. Lancet **2:** 241 (Aug. 6), 1949.

A 16 year old girl gave a history of dyspnea, severe pain in the middle of the sternum, and bouts of vomiting which were initiated thirty-six hours prior to admission to the hospital. She died twenty-four hours after admission. Necropsy showed that all chambers of the heart were much dilated. A large infarct ten to fourteen days old involved the lower part of the interventricular septum, the anterior part of the apices of the left and right ventricles and the posterior part of the left ventricle. In the area of in-

farction one of the posterior branches of the left coronary artery contained a thrombus. The lungs were bulky, firm and very edematous, and there was a hemorrhagic area in the left lung, under which was found a moderate-sized infarct, probably two to three days old.

BELLET

ELECTROCARDIOGRAPHY

Zuckermann, R., Cabrera Cosio, E., and Bisteni, A.: The U Wave. Arch. Inst. Cardiol. de Mexico **19:** 246 (April 30), 1949.

In twenty-one electrocardiograms taken from a series of 2,500 consecutive tracings (0.84 per cent), the deviation of the axis of the U wave suggested left "strain" in 19 cases and right "strain" in 2 cases. In 19 of the cases, the only indication of "strain" was the anomalous U wave. In 2 cases the U wave confirmed the diagnosis of "strain" suggested by other phenomena. Since anomalies of the U wave may enable one to suspect or confirm the diagnosis of left or right "strain," the author feels it is necessary to pay more attention to this wave of the electrocardiogram.

LUISADA

Friedland, C., Sodi-Pallares, D., Soberon, J., and Fishleder, B.: The Electrocardiogram in the Differential Diagnosis of Rheumatic and Luetic Aortic Insufficiency. Arch. Inst. Cardiol. de Mexico **19:** 341 (June 30), 1949.

In order to elicit electrocardiographic signs of aid in the etiologic diagnosis of aortic insufficiency, the histories, autopsy reports, and electrocardiograms of 32 patients with luetic aortic insufficiency and 42 patients with rheumatic aortic insufficiency were studied. The authors found that the presence of incomplete left bundle branch block suggests a luetic etiology and that notching and slurring of P, if particularly marked, suggests a rheumatic etiology.

LUISADA

Bellet, S., Nadler, C. S., Gazes, P. C., and Lanning, M.: Effect of Vomiting due to Intestinal Obstruction on the Serum Potassium. Am. J. Med. **6:** 712 (June), 1949.

The authors studied the electrocardiographic findings in 15 cases of acute intestinal obstruction accompanied by vomiting. They compared the electrocardiographic changes with serum potassium levels and determined the effect of administration of potassium upon these changes. Hypopotassemia is associated with electrocardiographic changes consisting of a lengthening of the Q-T interval, depression of the S-T segment and, in some instances, inversion of the T waves. A correlation was observed between the severity of these changes and the degree of hypopotassemia.

It is pointed out that the diagnosis of potassium deficiency depends on the recognition of conditions likely to be associated with this disturbance, the presence of muscular weakness and occasional muscular paralysis, the typical electrocardiographic changes which return to normal with potassium administration, and confirmation by determination of the serum potassium. It seems very probable that some of the symptomatology of intestinal obstruction may be the result of a deficiency of potassium. This concept is based on the known depletion of potassium following vomiting, the asthenia, weakness, low blood pressure and shock-like state, the marked electrocardiographic changes, and the rapid restoration of the electrocardiogram to normal and the improvement of the symptoms of intestinal obstruction following administration of potassium. The loss of potassium in intestinal obstruction is mainly by way of long continued vomiting of gastrointestinal secretions with resultant loss of intra- and extracellular fluids. Additional diminution of serum potassium may result from procedures such as gastrointestinal suction, and parenteral administration of glucose designed to treat the symptoms of intestinal obstruction.

The experience of the authors tends to indicate that patients with low potassium levels can tolerate large quantities of potassium salts without untoward effects. It is suggested that in case of doubt, injections be given slowly and frequent electrocardiographic checks be made before additional quantities are administered.

SCHWARTZ

Dietrich, H.: Anteroseptal Infarction of QIII-TIII type. A Contribution to the Clinical Diagnosis of Antero-Septal-Posterior Infarction with Perforation of the Septum. Ztschr. f. Kreislaufforsch. **38:** 415 (July), 1949.

A case is presented of a 60 year old woman with the typical history and clinical course of myocardial infarction whose death occured after admission to hospital. A very loud systolic murmur maximal in the fourth intercostal space, of unknown duration and persistent throughout the observation together with the electrocardiogram (QS waves and S-T elevation in Lead III and in CR_{1-4}), suggested perforation of the intraventricular septum due to infarction. This diagnosis was confirmed at autopsy.

PICK

Spang, K.: On the Vector Theory of the Chest Electrocardiogram. Remarks Concerning the Theoretical Basis of Thoracic Electrocardiography. Ztschr. f. Kreislaufforsch. **38:** 405 (July), 1949.

The author criticizes Wilson's assumptions that an "indifferent" electrode represents practically a zero potential and that a "unipolar" chest lead reflects potentials of the area underlying the electrode. In the author's opinion, which is based on

experimental work of several European authors, no unipolar lead exists in electrocardiography. There is no fundamental difference in the genesis of an electrocardiogram taken by bipolar extremity leads and by chest leads. Both represent the projection of simultaneous cardiac vectors upon different planes. The author argues that with Wilson's concept a similar QRS pattern should be expected in right- and left-sided chest leads. A tall R wave in V_1 and V_2, described as characteristic of right ventricular hypertrophy, was not found in cases where this hypertrophy was shown by autopsy, and was present in cases with nothing more abnormal than a vertical position of the heart. When chest leads are taken of exactly opposite points, mirror image patterns are obtained. S-T deviations in the standard leads sometimes fail to show up in the chest leads.

The author concludes that any chest lead is a mixture of both "dextro- and levocardiogram." The peak of the R wave in a chest lead cannot be considered as an intrinsic deflection and a QS wave is not due to a window effect of an infarcted area. The pattern of QRS and ST-T in a single lead depends merely on the projection of the respective vectors upon the electrodes representing this particular lead. The aim of further research in electrocardiography should be to find leads with optimal projection of normal and abnormal vectors.

PICK

Rigdon, R. H., and Ruskin, A.: Lethal Effects and Electrocardiographic Changes Produced by Quinine Dihydrochloride in Malaria-Infected Monkeys. J. Lab. & Clin. Med. **34:** 1109 (Aug.), 1949.

In this study, observations were made, first, to determine whether quinine dihydrochloride is fatal in smaller doses when given to monkeys with a severe malarial infection than when given to normal monkeys, and, second, to determine the electrocardiographic effects produced by quinine in these two groups of animals. The maximum amount of quinine that could be given to a normal monkey without producing death was about 55 mg. per kilogram of body weight. Ten malaria-infected monkeys died with doses of quinine varying from 20.8 to 41.3 mg. per kilogram of body weight. The malaria-infected monkeys that succumbed to the quinine had severe anemia and usually a high degree of parasitemia.

The electrocardiographic effects of quinine given intravenously in both normal and infected monkeys were usually maximal immediately after the completion of the injection. All the measurable time intervals returned to normal in six to thirty minutes except for the Q-T interval, which remained prolonged for varying periods in both normal and infected monkeys. In general, the same doses of quinine caused more marked effects in the electrocardiogram when the monkeys were infected and the greatest effects were produced in the more anemic animals. The electrocardiograms in monkeys who died showed increasing intraventricular block and ventricular slowing and asystole.

The data indicate that a monkey with a severe malarial infection is more susceptible to quinine than a monkey with a less severe malarial infection. It would appear that the susceptibility to quinine is related more closely to the anemia than it is to the degree of parasitemia.

MINTZ

Parry, Thomas M., Spencer, Joseph N., Whitehead, Richard W., and Draper, William B.: Studies on Diffusion Respiration. VIII. Changes in the Heart Rate, Blood Pressure and Electrocardiogram in Dogs During Diffusion Respiration. Anesthesiology **10:** 615 (Sept.), 1949.

On the basis of fifteen experiments carried out on dogs, the authors discuss the behavior of the circulation with respect to heart rate, blood pressure, and the electrocardiogram during "diffusion respiration." This type of respiration is accomplished by cannulating the trachea of the dog and partially denitrogenating the animal by allowing it to breathe pure oxygen for fourty-five minutes; administering 1/150 grain of atropine subcutaneously before each experiment and heparin at irregular intervals throughout the experiment; and producing and maintaining apnea through administration of an overdose of one per cent Pentothal sodium or a combination of Intocostrin and Pentothal sodium.

The establishment of "diffusion respiration" was not followed by any very significant or consistent changes in the heart rate. During the first five minutes of diffusion respiration there was a fall in the systolic blood pressure. This was followed by a gradual return of the blood pressure toward normal as the respiratory arrest continued, and, with the reestablishment of ventilation of the lungs, to a level above normal. The most evident change noted in the electrocardiogram was the appearance of ventricular extrasystoles during the first half of the period of diffusion respiration. These disappeared by the thirtieth minute of respiratory arrest. A progressive rise in the amplitude of the T wave was also noted as respiratory arrest continued.

The authors note that if extrasystoles appeared, they disappeared in the later phase of the experiment when the carbon dioxide content of the blood had risen to high levels. Thus, a marked lowering of the hydrogen ion concentration of the blood due to retention of carbon dioxide does not necessarily produce a serious disturbance of cardiac rhythm. Under the conditions of the experiments, the heart exhibited a remarkable degree of tolerance to acidosis. However, the authors emphasize that diffusion respiration does involve a definite hazard.

BELLET

HYPERTENSION

Haxton, H. A.: Chemical Sympathectomy. Brit. M. J. **4614:** 1026 (June 11), 1949.

The author reports experiences with nonoperative interruption of sympathetic activity by the use of paravertebral injections of aqueous phenol (a 10 per cent solution had a more lasting effect than a 6 per cent solution) in the treatment of vascular disorders in the lower extremities in 220 patients. In more than 90 per cent of cases a warm and dry foot was obtained and in 60 per cent the effect was a lasting one. In some cases in which the effect did not persist the injection was repeated and a good and lasting result obtained. Complications were few, consisting for the most part of some irritation of the genitofemoral nerve.

The author feels that the procedure of sympathetic interruption by the injection of aqueous phenol has much merit. Like an open operation, it results in destruction of the ganglion cells. Compared with operation, however, it is a relatively minor ordeal for the patient. Moreover, the treatment can be employed in cases in which operation is considered unjustifiable. Also, the method has the merit that it can be easily and rapidly repeated if necessary. In competent hands the method is a safe one, but the untried and untrained operator could easily cause serious complications. The following conditions have been successfully treated: hyperidrosis, erythrocyanosis and perniosis, arteriosclerosis, and any venous insufficiency.

BELLET

Loofbourow, D. G., Galbraith, A. L., and Palmer, R. S.: The Effect of the Rice Diet on the Level of the Blood Pressure in Essential Hypertension. New England J. Med. **240:** 910 (June 9), 1949.

The authors present a progress report on a study of the rice diet as a method of treatment for hypertension. They used a group of ambulatory clinic patients observed once a week while living in their normal surroundings and eating with other members of the family who were on a regular diet. The patients had essential hypertension with and without renal involvement.

The method used in evaluating blood pressure response was to list all pretreatment clinic blood pressures of a particular patient in numerical order, choosing the median value, and repeating this on the records taken during and after treatment. A reduction of 20 mm. Hg in median diastolic pressure was used to indicate an improvement. On this basis, 6 out of 16 patients, or 37 per cent of those strictly on the rice diet, showed an improvement in blood pressure. In the group of moderate adherers, 3 out of 20 patients, or 15 per cent, demonstrated improvement.

Considering 10 pounds as significant weight change, the authors found that 7 out of 16 strict adherers showed a significant loss of weight. Of this number, 4 demonstrated a diastolic drop of 20 mm. Hg or more. Of 20 moderate adherers, 5 showed a significant weight change, and only one of the 5 showed an improvement in blood pressure. However, the authors state that no valid conclusion about the correlation of weight reduction and change in blood pressure can be drawn from such a small group.

BELLET

Goldman, M. L., Kriss, J. P., Futcher, P. H., and Schroeder, H. A.: The Transfusion of Arterial Hypertensive and Normotensive Blood into Hypertensive Subjects. Am. J. M. Sc. **217:** 637 (June), 1949.

Six hypertensive patients were transfused with blood from other hypertensive patients and later with normotensive blood. The renal plasma flow and glomerular filtration rate were measured in 5 patients, and blood pressure in 5, before, during, and after transfusion.

No consistent changes were noted in glomerular filtration, renal plasma flow, or filtration fraction following the transfusions, although in some cases differences did occur. Relative to the changes produced by normotensive blood, hypertensive blood lowered mannitol value, PAH, and filtration fraction in one subject; it elevated the mannitol value in another; and it elevated the PAH clearance and depressed the filtration fraction in a third. When experiments on subjects with diminished renal function were done, the results were not consistent, although changes in the clearances of mannitol, PAH, or in the filtration fraction occurred in 2 patients. Hypertensive blood tended to elevate the diastolic blood pressure of the recipients to a greater extent than did normotensive blood. These experiments suggest, but do not prove, the presence of pressor substances in the arterial blood of hypertensive individuals.

DURANT

Byrom, F. B., and Dodson, L. F.: The Mechanism of the Vicious Circle in Chronic Hypertension. Clin. Sc. **8:** 1 (July), 1949.

Renal artery clamps were applied to previously unilaterally nephrectomized rats. As time went on sustained hypertension developed. Both cardiac and cerebral "vascular crises" appeared. After periods varying from four and one-half to thirty-two weeks the arterial clips were removed. With one exception, in 34 animals the blood pressure returned to normal within twenty-four hours. There was a prompt relief of symptoms referable to the hypertension. Histologic examination at least one month later revealed an essentially normal kidney. In many instances, the heart was less hypertophied than in rats dying before the arterial clamp was removed.

The authors conclude that within the time limits of this experiment, chronic renal hypertension in

rats with one kidney and the symptoms and lesions attributable to such hypertension are dependent on renal ischemia. This is in contrast to their previous finding that removal of the single renal artery clamp when both kidneys are present often failed to abolish the hypertension or to arrest the progress of arterial disease. They found no evidence of an independent extra-renal pressor mechanism, and it is suggested that the hypertension in the intact rat is maintained by damage inflicted on the unclamped kidney by the hypertension.

WAIFE

PERIPHERAL CIRCULATORY FAILURE

Hesselschwerdt, D. W., and Medbury, S. E.: Circulatory Collapse Following the Combined Use of Pituitrin and Pentothal. Anesthesiology **10:** 544 (Sept.), 1949.

The authors present reports of 2 patients in whom severe shock developed when the combination of pituitrin and Pentothal was administered. They state that there were two factors producing myocardial anoxia in these patients: pituitrin acting through coronary constriction, and Pentothal acting through direct myocardial depression. Together, they may produce shock.

The authors state that if the condition should present itself the corrective treatment consists of oxygenating the patient and administering epinephrine or ephedrine to counteract specifically the coronary constriction. To avoid its development, pitocin, the oxytocic factor, or ergonovine would seem to be a more suitable drug than pituitrin for obtaining the desired effect.

BELLET

Schroeder, H. A.: Renal Failure Associated with Low Extracellular Sodium Chloride: The Low Salt Syndrome. J.A.M.A. **141:** 117 (Sept. 10), 1949.

The syndrome of salt depletion has been observed in patients treated by low-salt diet, particularly when there has also been abundant water intake or overenthusiastic use of mercurial diuretics, and in patients who have lost excessive amounts of body fluids which have not been adequately replaced. The condition is characterized by progressive oliguria, a marked decrease in urinary chlorides, rapid weight gain, progressive azotemia, and hypochloremia and hyponatremia. Symptomatically, there may be weakness and lethargy, loss of appetite, thirst, nausea and occasional vomiting, and muscular cramps.

Twenty-one cases of the low-salt syndrome are analyzed. Ten patients died and 11 recovered, either spontaneously or as a result of treatment; of those who recovered, 4 subsequently died of a similar episode.

The pathogenesis of the disorder is as yet obscure, but the authors hypothesize that marked salt depletion brings about in some way, perhaps by cellular overhydration, either a reduction in renal blood flow or excessive tubular reabsorption of both salt and water. Uremia results.

The therapeutic value of hypertonic sodium chloride solution is stressed.

HANNO

RELATION OF ENDOCRINES TO CIRCULATION

Goodwin, J. F.: Thyrotoxic Auricular Fibrillation Treated with Thiouracil. Brit. M. J. **4611:** 895 (May 21), 1949.

The author reports on the effect of treatment of cases of auricular fibrillation due to thyrotoxicosis with thiouracil and discusses the value of certain associated factors in assessing the likelihood of reversion to sinus rhythm without additional therapy.

Of a series of 144 thyrotoxic patients, 28 had auricular fibrillation. All had been treated with thiouracil compounds for not longer than two years, and were cases of secondary thyrotoxicosis. Two patients were excluded from analysis because the thyrotoxicosis was not brought under control. Thirteen patients reverted to sinus rhythm with thiouracil treatment. (The average amount of thiouracil compound given was 50 mg. daily). In 13 patients, the thrytoxicosis was well controlled but the fibrillation persisted. Electrocardiographic abnormalities were present in 2 out of 11 patients in the former group and 4 out of 9 in the latter. These results indicate that reversion to sinus rhythm may be expected from thiouracil treatment alone in approximately 50 per cent of cases, and show that thiouracil compounds are at least as effective as surgery in this respect.

The author concludes that if sinus rhythm is not restored by thiouracil alone after a maximum period of four months, auricular fibrillation may become permanent unless other measures are taken. In these circumstances it is suggested that quinidine should be given to restore sinus rhythm if the thyrotoxicosis is under control. If thyrotoxicosis has not been effectively controlled by thiouracil, alternative treatment should be considered. There appears to be no reliable method of gaging the prospect of stopping fibrillation with thiouracil alone in any given patient, but the presence of electrocardiographic abnormalities indicating associated cardiovascular disease lessens the chance of reversion. Sinus rhythm is also less likely to return if the patient has a history of symptoms for more than four and one-half years before treatment. It is possible that digitalis tends to establish the arrhythmia, and its use should be avoided except where there is associated congestive heart failure.

BELLET

RHEUMATIC FEVER

Urnblad, S., Malmiros, H. and Urlander O.: Studies on Pathogenesis of Rheumatic Fever. II. Antistreptolysin Titre in Acute Tonsilitis. Acta med. Scandinav. **133:** 358 (June 14), 1949.

The antistreptolysin titer was studied in 96 cases of rheumatic fever. Elevated titers were found in 89.6 per cent of the cases. The titers registered during the course of the disease were higher than those plotted in the antistreptolysin curve in acute tonsilitis without rheumatic sequelae. The antistreptolysin curve was also more gradual in ascent and the elevated titer more prolonged in acute rheumatic fever. A certain parallelism was demonstrable between the erythrocytic sedimentation rate (ESR) and the antistreptolysin titer (AST). The ESR became abnormal earlier than AST with the onset of rheumatic fever and became normal earlier than the AST during the subsidence of the rheumatic episode.

The production of a higher antibody titer in rheumatic fever than in tonsilitis may be ascribed to the fact that patients with the former disease have been immunized and therefore can more easily produce the antibody in question. Serologic studies support the theory that the outbreak of rheumatic fever is preceded by repeated streptococcal infections. These infections may produce a hyperergy which is clinically manifested by rheumatic fever.

LECKS

Hench, P. S.: Potential Reversibility of Rheumatoid Arthritis. Ann. Rheumat. Dis. **8:** 90 (June), 1949.

Clinical and investigative observations are cited to show that rheumatoid arthritis is not necessarily a relentless, chronic, progressive condition which will never have a satisfactory method of control. Rheumatoid arthritis has subsided spontaneously, accidentally (anesthesia and surgical operations), and therapeutically. Chrysotherapy has induced remission in only about 10 to 15 per cent of cases. From a combined program of therapy (gold, physical therapy, removal of foci of infection, rest, and nutritious diet), striking results are promptly obtained in not more than about 15 per cent of cases.

When these results are compared with the effects of pregnancy which induces articular remissions of 60 to 90 per cent of cases, it is obvious that there is a great unrealized potential for the relief of rheumatoid arthritis. It is this potential which the authors wished to bring to reality.

LECKS

Costero, I.: Cerebral Lesions Responsible for Death of Patients with Active Rheumatic Fever. Arch. Neurol. & Psychiat. **62:** 48 (July), 1949.

The author states that in the brains of rheumatic patients vascular lesions are frequently observed which are responsible for death. He found that during the developmental periods of rheumatic fever the capillary vessels are always profoundly altered throughout the brain. These alterations consist chiefly in dilatation of the lymphatic perivascular space and collagenous transformation and hyalinization of the reticulum, with production of capillary sclerosis. The dilatation of the lymphatic space corresponds to an increase in the permeability of the capillary endothelium.

The author also states that the cerebral hemorrhages of patients with active rheumatic fever are related to the increase in permeability of the capillaries. Most frequently they are produced by diapedesis, while others are due to diabrosis of the endothelium. It is difficult to find zones of normal microglia in the wet brain of rheumatic patients. Commonly, the Hortega cells increase their cytoplasm and retract their expansions, and more of them than usual attach themselves to the capillaries; they also lose their characteristic spinous processes. Surrounding the areas of devastation, and in some apparently normal areas of the brain, the microglia acquires the modality of rod cells, while the same focus appears densely invaded by pseudopodal forms of microglia, a few hypertrophic fibrous astrocytes, and nets of precollagen fibrils.

In addition to these lesions, certain nodules of branching microglia were found by the author. The number of nodules seems to be independent of the extent and intensity of other cerebral lesions. The author considers it possible that the nodules of branching microglia cells represent a hyperergic reaction similar to that responsble for the Aschoff nodule in the connective tissue and that, therefore, they may be useful in the histopathologic diagnosis of the cerebral lesions during the evolutive period of rheumatic fever.

BELLET

Rubbo, S. D., Holmes, M. C. and Stokes, H. L.: Prophylactic Sulphanilamide in Rheumatic Fever. Lancet **2:** 311 (Aug. 20), 1949.

Small daily doses of sulphanilamide were given continuously to 211 children aged 4 to 14 years for 565 person-years. Over the same period 337 children were observed as controls for 971 person-years.

The results of the study showed the expected recurrence-rate for children aged 4 to 14 years to be 11.8 per cent, and that prophylaxis reduced this figure to 3.2 per cent. The authors believe that continuous prophylactic sulphanilamide administered in doses of 1 gram daily to ambulant patients who have had one or more attacks of rheumatic fever will significantly reduce the risk of further recurrence. Studies of organisms recovered from throat swabs showed a lowered incidence of group-A streptococcal carrier-rate among the treated patients. Carrier-rates for groups C and G were unaffected. No patients experienced major toxic reactions, but the authors do not recommend chemoprophylaxis unless patients can be observed at regular intervals.

From the results of tests on 669 strains of hemolytic streptococci there was an increase in the number of sulphanilamide-resistant forms isolated from the treated group. The authors state, however, that the development of resistant strains cannot increase the infection-rate since the incidence of infection is independent of this factor. Penicillin provides a substitute in case of manifest infection.

The authors observe that, in order to escape the untoward reactions which may arise if treatment starts in the acute phase, prophylaxis should be instituted when a quiescent state has been reached after a major episode, preferably after the first attack.

BELLET

ROENTGENOLOGY

Marchal, M.: A New Method of Radiologic Study of the Heart and Lungs, and its Applications to the Tumors of the Mediastinum. J. de radiol. et d'electrol. **30**: 305 (May–June), 1949.

The application of electrokymography to a mediastinal mass adjoining the right atrium indicated differences in the type of pulsation above and below, and ruled out an aortic aneurysm and aneurysm of the sinus of Valsalva. By observing the time relationships of pulsations to the R wave of an electrocardiogram it is possible to differentiate intrinsic from transmitted pulsations. The author also applies this technic to smaller pulmonary arteries, invisible other than by changes in density (densitometry).

SCHWEDEL

Arendt, J., and Cardon, L.: The Diagnosis of Intra-Auricular Thrombosis in the Living. Radiology **53**: 371 (Sept.), 1949.

Soft mural thrombi, as well as those which have calcified, can, under certain conditions, be recognized in standard roentgenograms of the heart. In a series of 771 necropsied patients with all types of heart disease, the incidence of intra-auricular thrombosis was 34.4 per cent. Few have been recognized clinically and still fewer roentgenographically. An intra-auricular thrombus can be recognized roentgenographically when it is of sufficient size or when it is impregnated with calcium. The noncalcified soft mural thrombi are more difficult to diagnose.

The author stresses the roentgen finding of a prominent third left arc along the left lateral cardiac contour immediately above the upper demarcation point of the left ventricle, as seen in the posteroanterior projection, as being strongly suggestive of a thrombus in the left auricle. This bulge usually represents the left auricular appendage; when this is prominent, auricular thrombi are frequently present. Even though many competent observers believe this curve represents a prominent pulmonary conus, the author believes that the evidence contributed by kymography and angiocardiography demonstrates that the left auricular appendage forms a substantial part of this curve. He cautions that right heart enlargement with subsequent counterclockwise rotation of the heart may displace the left auricular appendage backward; the conus segment then appears on the left contour of the heart.

ZION

Liverud, K.: Tuberculoma Simulating Cardiac Aneurysm or Localized Pericardial Effusion. Acta Radiologica **32**: 73 (VII), 1949.

The author presents a case with protuberance in the region of the upper left ventricle which increased in size over a seven year period. At autopsy a tuberculoma was found covering the pericardium in the affected region.

SCHWEDEL

SURGERY AND THE CARDIOVASCULAR SYSTEM

Walker, A. J. and Barcroft, H.: Return of Tone in Blood-Vessels of the Upper Limb after Sympathectomy. Lancet **25**: 1035 (June 18), 1949.

The authors recorded the blood-flow in the hand with the plethysmograph prior to and daily for about two weeks after sympathectomy. Experiments were made on fourteen sympathectomised hands; five were operated on for excessive sweating and nine for vascular disease.

In every case the most rapid flow was recorded either immediately after sympathectomy or on the following day. The flows through the five hands with normal vessels were generally greater than those through the nine hands with diseased vessels. Blood flow in all hands decreased rapidly during the remainder of the first week and more slowly during the second. Tone returned to the diseased vessels at much the same rate as to the normal ones.

The authors state that the very large postoperative blood flow was not caused by vasodilator substances released by the trauma of the operation or by postoperative pyrexia. The results indicate absence of any relation between temperature of the air in the plethysmograph and the rate of the blood flow in the hand. The behavior of the blood flow after ganglionectomy appears to have been just the same as that after preganglionic section. The authors state that finger temperatures are not related to the blood flow in the hands; nevertheless, they conclude that recovery of tone after sympathectomy must have taken place to a large extent in the vessels of the fingers, though it was not apparent from the results of the skin temperature readings.

BELLET

Lyon, R. P., Stanton, J. R., Freis, E. D., and Smithwick, R. H.: Blood and "Available Fluid" (Thiocyanate) Volume Studies in Surgical Patients;

Part 1. Normal Patterns of Response of the Blood Volume, Available Fluid, Protein, Chloride, and Hematocrit in the Postoperative Surgical Patient. Surg., Gynec. & Obst. **89:** 9 (July), 1949.

Twenty patients, the subjects of major surgical procedures, were studied preoperatively and throughout an eight to ten day period following operation. Definite patterns of response were noted postoperatively in the blood, "available fluid," plasma, and red cell volumes as well as in the plasma protein concentration, hematocrit, and total circulating protein.

Following blood loss, the mechanism for the preservation or restoration of the total blood volume appears to be dependent upon a state of positive fluid balance. With patients in negative fluid balance following operation, recovery of the "available fluid," plasma, and total blood volumes was delayed until a state of positive fluid balance was established. In the absence of excessive extrarenal water and salt loss, a daily ration of two to three liters of five per cent glucose in water under the conditions of this study was adequate to establish positive fluid balance and to insure plasma volume recovery. When depleted through either operative or postoperative blood loss, the red cell volume showed little tendency to recover spontaneously within the first ten days following operation. In the adequately hydrated patient, serial determinations of the basal hematocrit offered the most useful index of uncompensated blood loss. Postoperative decreases in the plasma protein concentration of from 0.2 to 1.0 gram per hundred cubic centimeters were not necessarily indicative of either inadequate nutrition or a depleted total amount of circulating protein.

The influence of the state of hydration and amount of blood loss on the patterns of response of these volumetric compartments and concentration measurements is described and the significant interrelationships are discussed.

BECK

Gullickson, M. J., McRae, J. H., and Campbell, D. A.: Vagovagal Reflexes. Surg., Gynec. & Obst. **89:** 153 (Aug.), 1949.

Because instances of sudden death due to cardiac or respiratory arrest coincident with manipulation of a vagus nerve or its branches during surgery in the neck or thorax have been reported, the authors studied electrocardiographic alterations during the operation of vagotomy for duodenal ulcer. Bilateral vagotomy was performed on 10 dogs. No premedication was given and endotracheal ether anesthesia was employed during the experiments. In addition, electrocardiograms were taken in 10 patients before, during, and after bilateral vagotomy for duodenal or marginal ulcer. All electrocardiographic records taken in the period after induction of anesthesia and before beginning the operative procedure were normal.

On eleven occasions during the operative procedures on 5 animals, decreases in rate, changes in amplitude or inversion of the P wave, variations of the P-R interval, dissociation phenomena, or sinus arrhythmia and sino-auricular block were thought to have been specifically related to manipulations of the vagus. All changes observed during operation without exception reverted to normal simultaneously with, or shortly after, closing the chest. Lengthening of the P-R interval, apparently related to handling of a vagus nerve, occurred in 2 human subjects.

If electrocardiographic abnormalities were noted they usually occurred early in the operation; about the time that the first exploratory movements for the nerves were being made. When major changes in cardiac rhythm appeared, they exhibited a definite tendency to persist throughout the remainder of the operation, and additional manipulation of viscera or nerve trunks failed to induce further change.

The authors feel that the anesthetic sensitizes certain tissues, and the result is a response to stimuli which would otherwise be ineffective. Since stimulation of the gastric vagi seemed directly to initiate alterations in cardiac rhythm it is suggested that the vagi serve as the afferent path for some viscerocardiac reflexes.

BELLET

Holman, E. and Willett: The Surgical Correction of Constrictive Pericarditis. Surg., Gynec. & Obst. **89:** 129 (Aug.), 1949.

The authors discuss the indications for decortication, the surgical technic, and the results in a collected series of 265 cases of constrictive pericarditis. The best results are achieved in young persons in whom other organs are normal and in whom liberation of the compressed heart or its vessels is the only correction necessary. A satisfactory and adequate pericardiectomy must include liberation of all borders of the heart, and of both venae cavae. The inferior cardiac border must be liberated by excision of the pericardium lying between the heart and the diaphragm. Persistence of ascites following pericardiectomy is evidence of an inadequate decortication and demands reoperation and removal of more scar, rather than an omentopexy or Talma operation. The best evidence of an adequate operation is prompt and permanent lowering of venous pressure.

BECK

THROMBOEMBOLIC PHENOMENA

Adamson, D. L., Weaver, R. T., and Jaimet, C. H.: A New View on the Use of Dicoumarol in the Pregnant Patient. Canad. M. A. J. **61:** 6 (July), 1949.

The authors report a preliminary study of anticoagulant therapy administered to 15 pregnant women presenting a history and/or evidence of venous thrombosis. In their experience, the administration of the initial dose of dicumarol at onset of labor does not increase the loss of blood. They suggest that an anticoagulant should be given at once when there is any sign of venous thrombosis and also when an embolus occurs, and recommend further that it should be routinely administered, barring contraindication, when there is a history of previous thrombosis or embolism. The authors have adhered to the routine of giving dicumarol in a dose of 300 mg. with the first labor pain and continuing adequate dosage for at least ten days postpartum.

BELLET

Spitzer, J. M., Rosenthal, Norman, Weiner, Murray, and Shapiro, Shepard: Relation of Pulmonary Embolism to Peripheral Thrombosis. Arch. Int. Med. **84:** 440 (Sept.), 1949.

The authors report an analysis of the incidence of thromboembolism, according to postmortem diagnosis, in patients in a variety of age groups and with various types of disease. The data show that there was a lack of pulmonary embolism in patients with Laennec's cirrhosis, while, in the same patients, the incidence of cardiac and peripheral venous thrombosis was not particularly low. It is established that the coagulation mechanism is apt to be disturbed in chronic liver disease. However, the extent of hypocoagulability of the blood in such patients is not great. In considering the relation of disturbed coagulation to the development of thrombosis and to embolization, it is especially noteworthy that the incidence of the two phenomena is not parallel. Apparently the factors which determine the development of venous thrombosis are not necessarily responsible for the liberation of pulmonary emboli. In the group of patients over 70 years of age, the incidence of pulmonary embolism was 21 per cent. In those from 50 to 70, it was less than 7 per cent. There was no similar variation in the incidence of thrombosis. What is known of the conditions which are responsible for the formation of intravascular thrombi is inadequate to explain the variations in incidence of pulmonary embolism.

BERNSTEIN

Pagel, W.: Acronecrosis Due to Fibrin Thrombi and Endothelial Cell Thrombi. Am. J. M. Sc. **218:** 425 (Oct.), 1949.

Cyanosis followed by necrosis of the extreme parts of the periphery, such as the tip of the nose, the lobe of the ear or the tip of a finger, is an event well known to occur in subacute bacterial endocarditis. It is suggested that the term "acronecrosis" be adopted to describe this phenomenon. Its usual explanation by embolism from distant sites appears to be unsatisfactory in many cases in the light of the findings recorded in this paper. Three cases of subacute bacterial endocarditis are reported, in 2 of which small fibrin thrombi and endothelial cell thrombi in the venous sinuses of the skin are described as the cause of "acronecrosis," and, in the third, similar fibrin thrombi and endothelial cell thrombi were observed in the smaller branches of the pulmonary artery. Organization of these thrombi can lead to fibrinoid and hyaline thickening of parts of the vascular wall or to multipartition of a vessel. Necropsy and experimental evidence suggest that the vascular changes described are due to a hypergic response to antigenic stimuli.

DURANT

OTHER SUBJECTS

Eck, H.: So-called Specific Productive Myocarditis. Zentralbl. f. inn. Med. **4:** 331 (June), 1949.

The author describes the case of a 16 year old boy who developed fever and pain in the left chest one year before admission and showed, clinically, a diffuse enlargement of the heart with a systolic murmur over the pulmonary artery. The patient died suddenly. Autopsy revealed a heart which weighed 1,400 grams and showed in all sections, particularly in those from the wall of the right ventricle, tumor-like masses up to the size of a tangerine protruding above the surface. There was a complete obliteration of the pericardial cavity caused by adhesions. No evidence of syphilis or tuberculosis was found. Histologic examination revealed granulation tissue showing lymphocytes, plasma cells, and histiocytes but few eosinophile cells. There were areas of caseation and giant cells of the Langhans type. The blood vessels in the involved areas showed necrosis of the intima and media with fibrotic obliteration. The formation of the granulation tissue is considered to have been the primary process and an allergic-hyperergic reaction is assumed to have been responsible.

SCHERF

Schwartz, M.: Sudden Death from Tetraethylammonium Bromide. Lancet **256:** 1001 (June 11), 1949.

TEAB or the chloride (TEAC) has been used on several thousand patients, and is generally held to be quite harmless; but a few serious reactions have been observed. The author reports on the result of treatment of 7 cases of bronchial asthma with TEAB. No alarming side-effects were observed in 6 cases, but the seventh patient died immediately after the injection of TEAB. The immediate cause of death in this patient cannot be definitely established, but there is no reason to suppose that anything but the TEAB was responsible. The most likely explanation is a sudden excessive hypotension due either to lowering of the blood pressure or to

ventricular fibrillation. Probably the rate at which the injection was given (100 to 500 mg. in fifteen to sixty seconds) was of decisive significance.

The author concludes that use of TEAB in asthma does not seem to be particularly effective, and since it is attended by risk, it appears to be inadvisable.

BELLET

Gaddum, J. H., Peart, W. S., and Vogt, M.: The Estimation of Adrenaline and Allied Substances in Blood. J. Physiol. **108:** 467 (June 15), 1949.

Because no single test for estimating epinephrine and allied substances in the blood is specific, the authors made parallel quantitative analyses, using five sensitive methods. These included inhibitory effects on the uterus and colon of rats and the ears of rabbits, and excitatory effects on spleen and nictitating membrane of cats. If parallel quantitative assays of an unknown solution are made by the five tests, using adrenaline as a standard, and if these tests agree with a maximum error ratio of not more than two, it is reasonable to conclude that the effects of the unknown solution are due to adrenaline. Any other similar substance can also be identified in the same way, providing only one pharmacologically active substance is present in the solution. Thus, these tests seem to have the power of distinguishing closely allied sympathomimetic amines, in pure solutions. However, there is no simple way of estimating nor-adrenaline in the presence of similar amounts of adrenaline.

In applying these tests to blood, the effect of interfering substances can be avoided by collecting blood with much heparin in cool silicone-coated tubes and promptly removing the cells. If the cells are rapidly removed by centrifugation, adrenaline or nor-adrenaline can be identified in the plasma, if present.

WAIFE

Meltzer, V.: The Size of the Heart and the Adrenals in Guinea Pigs Following Exercise and Following Additional Treatment with Digitalis. Ztschr. f. Kreislaufforsch. **38:** 341 (June), 1949.

The author reports that young guinea pigs, after swimming daily for 150 minutes throughout a period of eight weeks, developed moderate hypertrophy of the heart and marked hypertrophy of the adrenals. Digitalis did not increase the efficiency of the exercised animals but the hypertrophy of both organs was more marked after this drug was administered. Digitalis administered to control animals produced no hypertrophy but it increased the adrenals to a size larger than that seen after exercise. The author suggests that an extracardiac regulation of organ hypertrophy by the growth hormone of the hypophysis seems probable.

PICK

Kattwinkel, E. E.: Death Due to Cardiac Disease Following the Use of Emetine Hydrochloride in Conditioned-Reflex Treatment of Chronic Alcoholism. New England J. Med. **240:** 995 (June 23), 1949.

A fatal case of myocardial damage after the administration of emetine in large doses is reported by the author. The drug was used in the conditioned-reflex treatment of chronic alcoholism in a healthy young man. This patient developed clinical evidence of toxic myocarditis and circulatory collapse. Necropsy revealed evidence of myocarditis of the type observed in emetine poisoning.

There is no known specific treatment for the cardiac damage due to emetine. Prevention is all important. The author suggests the following rules to govern the emetine treatment: (1) An electrocardiogram should be taken before, during and one or two weeks after treatment. (2) Suspected organic heart disease should contraindicate treatment. (3) The total dose of emetine should not exceed 0.6 Gm. in any one course. (4) At least two months should elapse between courses of treatment in patients who show any electrocardiographic changes during treatment. (5) When significant electrocardiographic changes occur, treatment should be stopped at once. (6) Signs of toxicity and dizziness should be carefully watched for daily, and if these develop the heart should be watched with great care. The prognosis in these cases is good if the early signs of cardiac damage have been heeded, since the pathologic process is reversible.

BELLET

Grossman, C.: Periodic Paralysis Associated with Obesity of Hypothalamic Origin. Arch. Neurol. & Psychiat. **62:** 105 (July), 1949.

The author observed an 18 year old girl who had three episodes of sudden gain in weight over a period of two years. Each time, she gained about 40 pounds in a few days, acquiring a picture of acute obesity with characteristic hypothalamic distribution. The last episode of a gain in weight was preceded by signs of diabetes insipidus and a severe attack of total paralysis of all voluntary muscles, with loss of reflexes and excitability to electrical stimulation. This was accompanied by a marked overactivity of the whole sympathetic system, loss of reaction of the pupils to light, lowering of serum potassium and electrocardiographic changes.

The author states that a diffuse hypothalamic "discharge" should be regarded as the underlying cause of the complex neuro-vegetative and metabolic manifestations. He remarked upon the close relation of the muscle paralysis to the variety of vegetative manifestations, such as prodromal severe thirst and polyuria, and concludes that it is reasonable to assume that these vegetative manifestations are of central origin and due to a dysfunction of arising in the hypothalamic region.

BELLET

AMERICAN HEART ASSOCIATION, INC.

1775 Broadway, New York 19, N. Y.

Telephone Plaza 7–2045

THIRTY-TWO RESEARCH AWARDS ANNOUNCED

The Board of Directors, on recommendation of the Research Committee of the Scientific Council, has approved research awards to two Established Investigators and thirty Research Fellows. The latter include seventeen awards for new Research Fellows, the renewal of twelve Research Fellowships, and the extension of another through March. The twenty-nine Research Fellowships, new and renewed, are for one year each; the awards for Established Investigators are each for five years.

The two Established Investigators named will be engaged in independent research, while the Research Fellows will work under mentors in various medical schools and hospitals.

The following have accepted the awards:

Established Investigators

Merrill, John P. The further development of the artificial kidney as a therapeutic and investigative tool in cardiovascular and renal disease; at Peter Bent Brigham Hospital.

Bloch, Edward H. A study of the living microscopic blood, blood flow and vessel walls in patients and experimental animals with thrombo-embolic phenomena; at University of Illinois.

Renewal Research Fellows

Brust, Albert A., Jr. Hypertension and vascular disease, under Eugene B. Ferris, Cincinnati General Hospital.

Fishman, Alfred P. Training in fundamental cardiovascular physiology and cardiovascular investigation, under Eugene M. Landis, Harvard Medical School.

Foltz, Elwood L. Studies on the coronary blood flow and related cardiac, metabolic and dynamic changes resulting from coronary narrowing, under Charles C. Wolferth, University of Pennsylvania.

Heller, John H. Vasoconstriction and hypertension; cholesterol and arteriosclerosis, under Francis G. Blake, Yale University.

Hurst, William W. Mechanisms of formation and removal of edema of cardiac origin—particularly water and electrolyte balance, under F. R. Schemm, Western Foundation for Clinical Research, Great Falls, Mont.

Jones, Richard J. The normal limits of the critically damped ballistocardiogram, their influence by the electrical axis of the heart, under Emmet B. Bay, University of Chicago.

Mark, Lester C. Cardiac arrhythmias; prevention and treatment, under Emery A. Rovenstine, New York University.

Olson, Robert E. The fate of C^{14}-labeled substrates in cardiac muscle from normal and vitamin-deficient ducklings and rats with attention to relationships between oxidation and high-energy phosphate bond generation (uptake P^{32}), under Fredrick J. Stare, Harvard University School of Public Health.

Schnabel, Truman G., Jr. Dynamics of the cardiovascular system by means of small plastic catheters, under H. C. Bazett, University of Pennsylvania.

Sommer, Leonard S. Cardiovascular physiology and pharmacology in dogs and humans, under Robert F. Loeb, Columbia University.

Sutton, George C. Extension under Professor E. Rothlin, Sandoz Pharmacology Laboratories, Basel, Switzerland, to March 31, 1950.

Tobian, Louis, Jr. The relationship of steroid substances and sodium to hypertension and toxemia of pregnancy; the effect of emulsifying agents on experimental atherosclerosis, under Carl A. Moyer, Southwestern Medical College.

White, Abraham G. The mechanism of edema formation following administration of electrolytes to congestive heart failure, under Louis Leiter, Montefiore Hospital, New York.

New Research Fellows

Aikawa, Jerry K. Immunophysiology of rheumatic fever and subacute bacterial endocarditis, under William J. Kerr, University of California.

Capps, Robert T. The response of the cardiovascular system to different methods of anaesthetic administration, under O. S. Orth, University of Wisconsin.

Crosley, Archer P., Jr., The application of renal physiology to the study of certain aspects of cardiovascular disease, under Francis C. Wood, University of Pennsylvania.

Edelman, Isadore S. Hormonal influences on the distribution and equilibrium times of electrolytes (Na^{24} and K^{42}) and water (D_2O) across cell membranes, under Francis D. Moore, Harvard Medical School.

Fortier, Claude. Neuro-endocrinological factors of arterial hypertension, under Hans Selye, University of Montreal.

Horlick, Louis. The physical properties of lipid particles in the blood and of the physiological and structural factors influencing them, under Kenneth A. Evelyn, McGill University.

Jorgens, Joseph. A study of the pulmonary pulsation curves, under Leo G. Rigler, University of Minnesota.

Kalbacher, Joseph E. The role of serum potassium in heart block of acute rheumatic fever, under Harold C. Anderson, Irvington House, Irvington, N. Y.

Miller, Joseph H. Development and application of a mechanical heart lung for intracardiac surgery in the human, under Harry Goldblatt, Cedars of Lebanon Hospital, Los Angeles.

Paterson, Philip Y. Relation of organ specific antibodies to demyelinating disease; relation of beta hemolytic streptococci to rheumatic fever, under Lewis Thomas, Tulane University of Louisiana.

Payne, Torrence P. B. A study of the local factors concerned in the development of atherosclerosis, under G. Lyman Duff, McGill University.

Peterson, Lysle H. Manometric study of cardiac events and elastic changes of vessels under normal exercise and pathological condition, under H. C. Bazett, University of Pennsylvania.

Ritzmann, Leonard W. The action of cardiac glycosides in different varieties of heart failure, under John McMichael, Postgraduate Medical School of London, England.

Roberts, Kathleen E. Studies in renal physiology and its relationship to cardiovascular disease with special emphasis on the regulation of potassium, sodium and extracellular fluid, under Robert F. Pitts, Cornell University Medical College.

Rosenman, Ray H. Hypertension, under Meyer Friedman, Mount Zion Hospital, San Francisco.

Schieve, James F. The homeostatic mechanisms regulating the arterial blood pressure, under Eugene A. Stead, Jr., Duke University.

Waugh, Douglas O. W. A study of cardiac, vascular and renal lesions produced in experimental animals by protein injection, under G. Lyman Duff, McGill University.

COURSE ON DISEASES OF THE BLOOD VESSELS

A course on Diseases of the Blood Vessels, excluding the heart, will be presented under the auspices of the American College of Physicians at the Cornell University Medical College and New York Hospital from March 13 to 18, 1950. This course will be under the direction of Dr. Irving S. Wright. Inquiries for matriculation should be addressed to Mr. Edward R. Loveland, Executive Secretary of the American College of Physicians, 4200 Pine Street, Philadelphia, Pennsylvania.

IMPORTANT NOTICE: PAPERS FOR INTERNATIONAL HEART CONGRESS, PARIS, SEPTEMBER 3–9, 1950

Doctor Paul D. White, Secretary pro tem of the International Cardiac Council, has announced the decision by the Council that titles and summaries (not exceeding 300 words) of papers offered for presentation at the First International Heart Congress in Paris next September should be sent in triplicate to the Secretary of each applicant's national heart association throughout the world.

A Committee of the American Heart Association has already been established to select the most suitable communications from the U. S. A. to be forwarded to the Inter-American Cardiac Committee and thence to the headquarters in Paris, where final selection will be made. The listing submitted by the American Heart Association Committee will be arranged on a priority basis. It is expected that 400 to 500 papers may be read at the meeting in Paris and that half of these will be allocated to the Western Hemisphere. Each communication is to take not over ten minutes, as a rule, followed by a five minute discussion period. These titles and summaries should be in the hands of Dr. Charles A. R. Connor, Medical Director, American Heart Association, 1775 Broadway, New York City, by March 1.

PAPERS REQUESTED BY INTER-AMERICAN CARDIOLOGICAL SOCIETY

Notice has been received from the Inter-American Cardiological Society, in Mexico City, that its active and affiliated members are requested, in accordance with the Society's by-laws, to send twelve reprints of their published works for redistribution among the constituent societies. Publications should be addressed to Dr. Teofilo Ortiz Ramirez, General Director, Sociedad Interamericana de Cardiologia, Instituto Nacional de Cardiologia, Calzada de la Piedad Num. 300, Mexico, D. F.